Nanocapsules: Calix[4]arene Derivatives that Self-Assemble through Ionic Interactions in Polar Solvents

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Nanocapsules: Calix[4]arene Derivatives that Self-Assemble through Ionic Interactions in Polar Solvents

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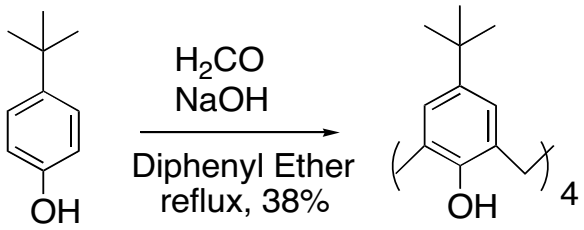
TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF EXPERIMENTALS



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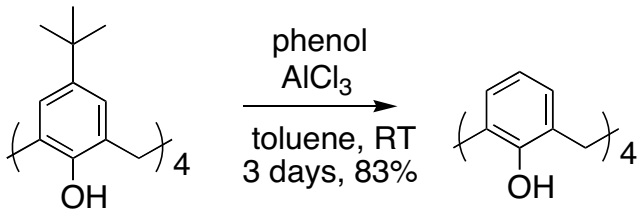

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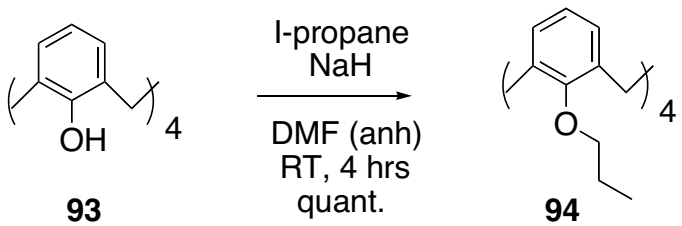

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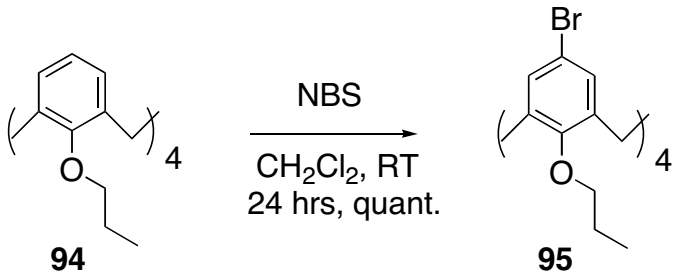

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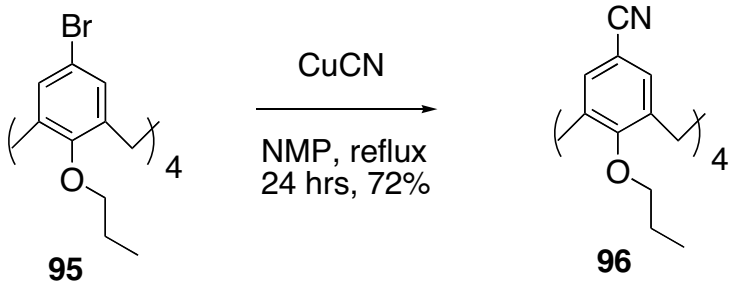

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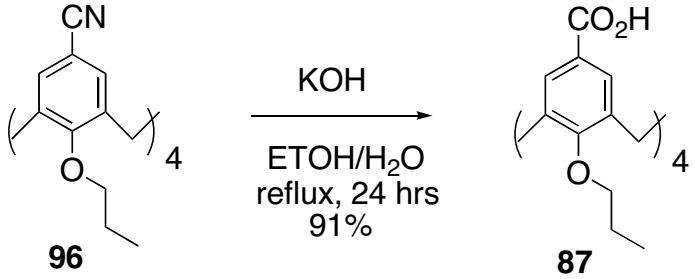

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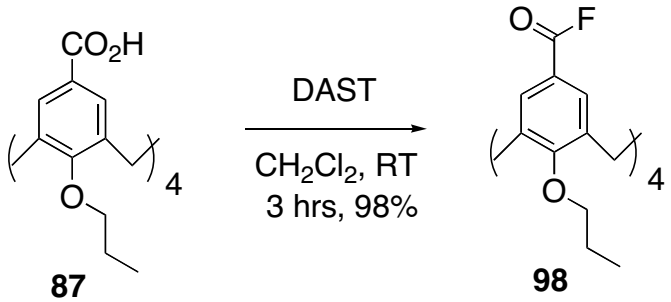

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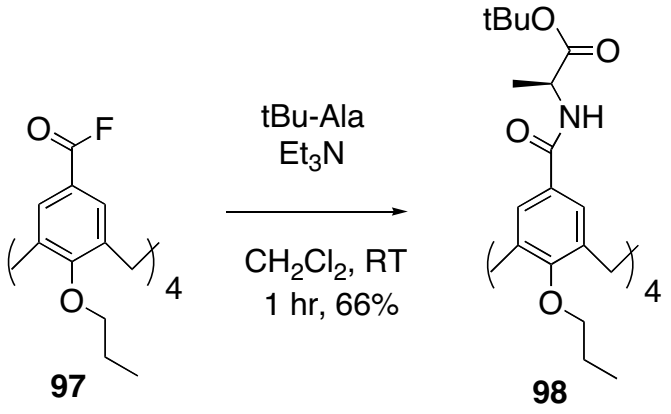

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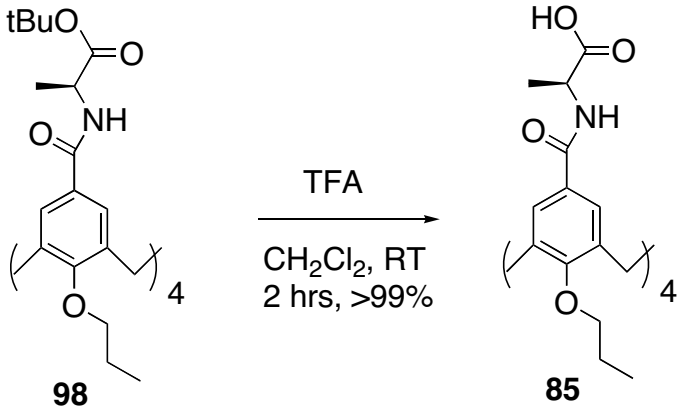

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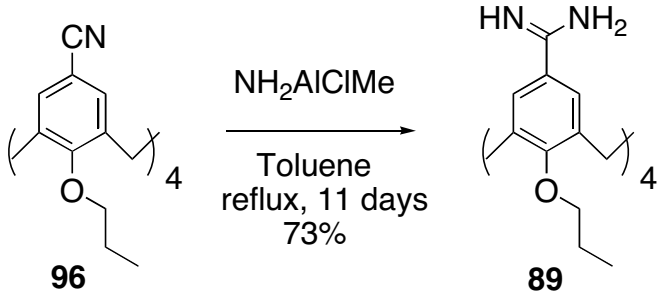

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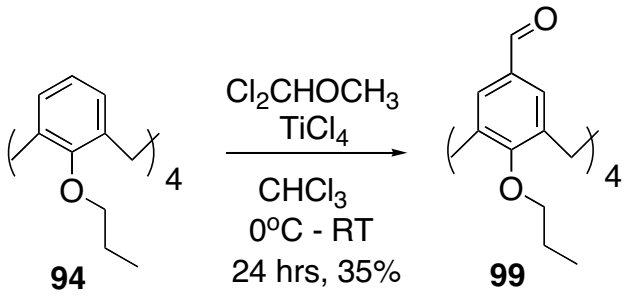

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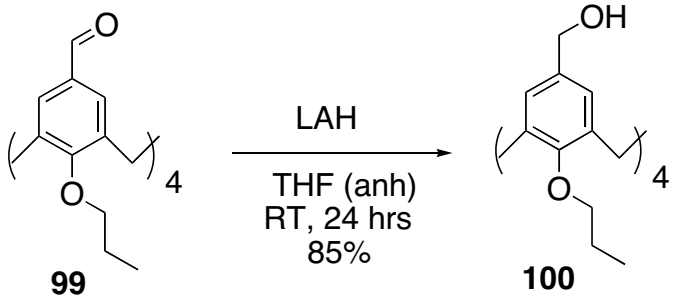

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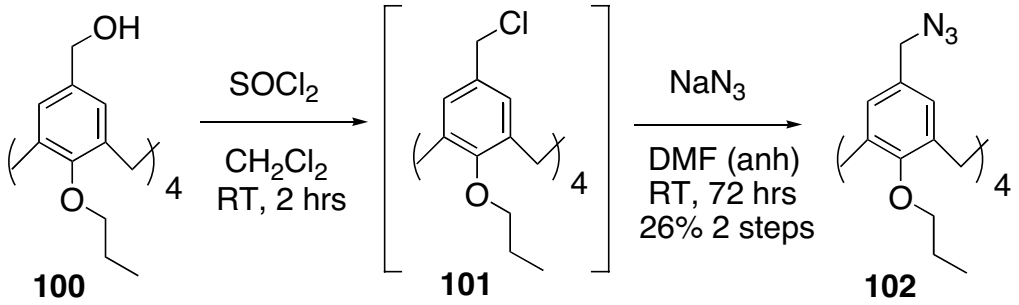

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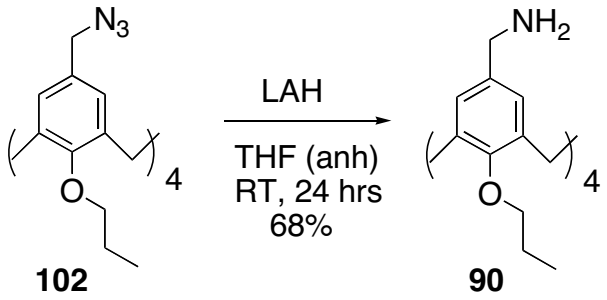

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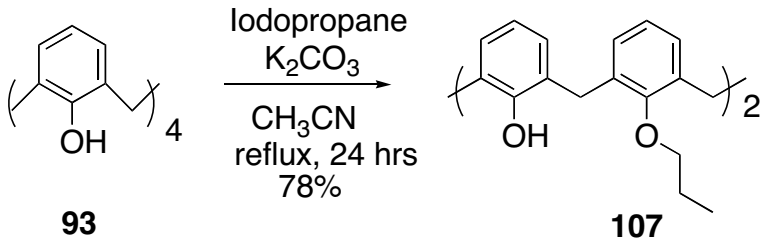

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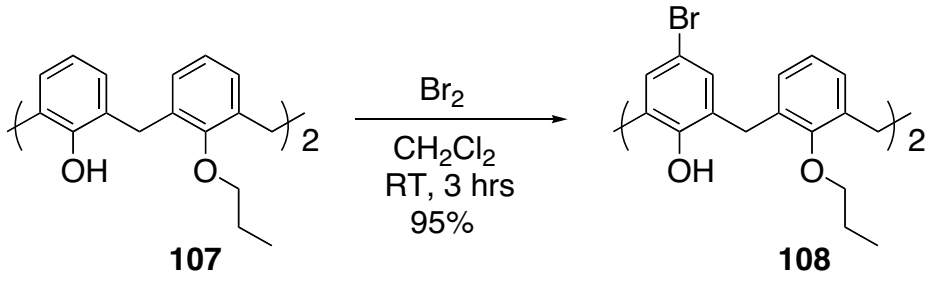

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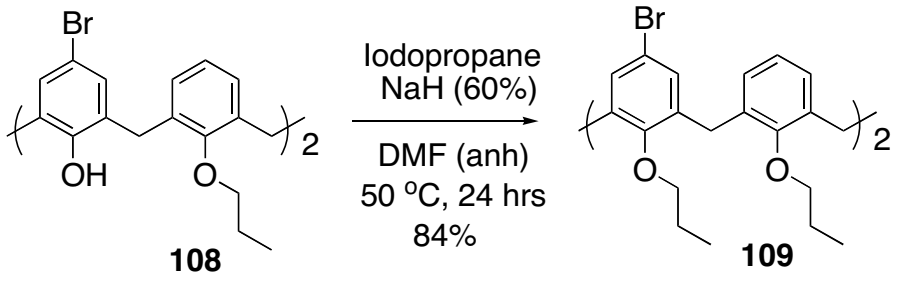

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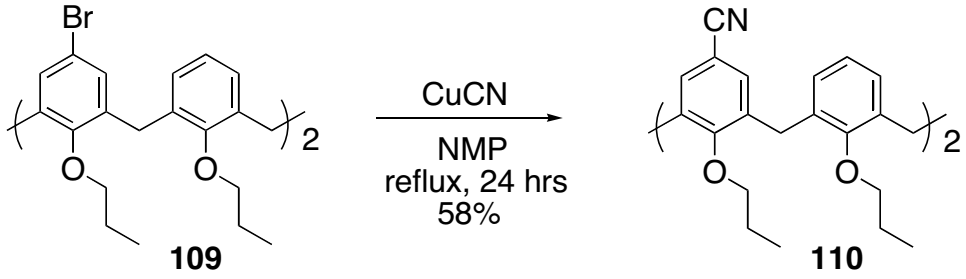

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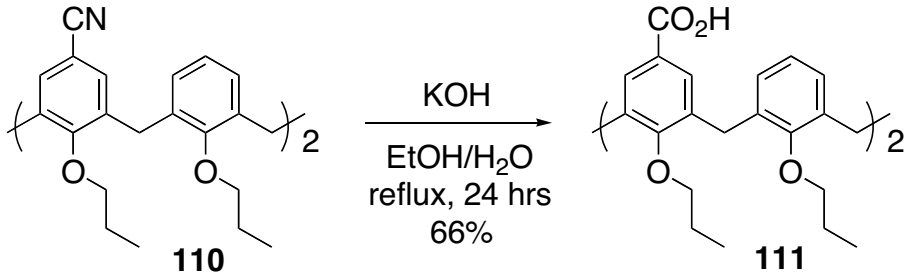

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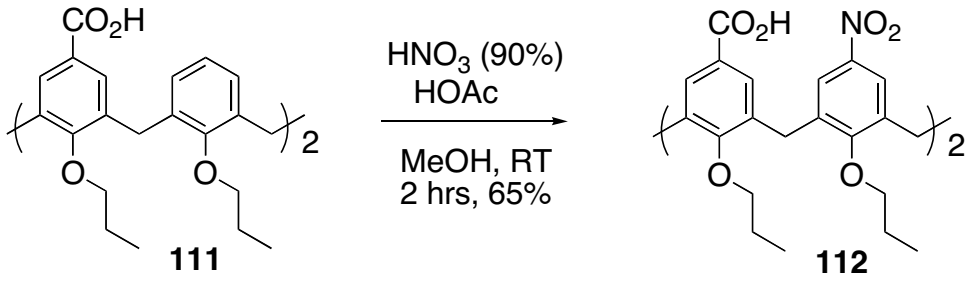

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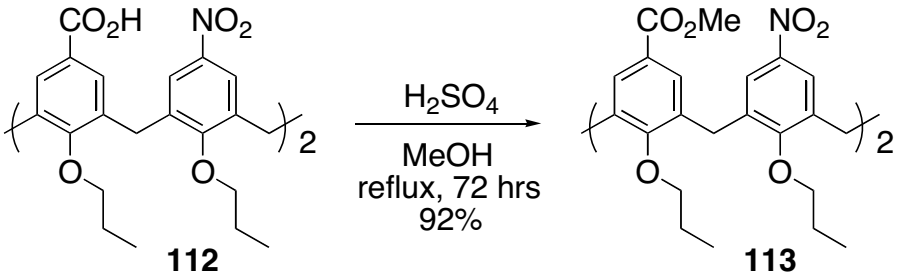

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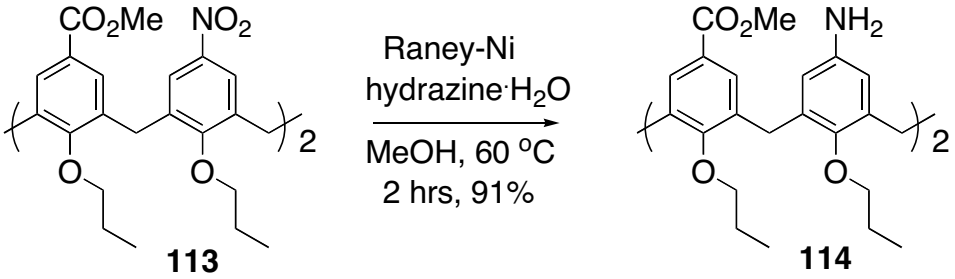

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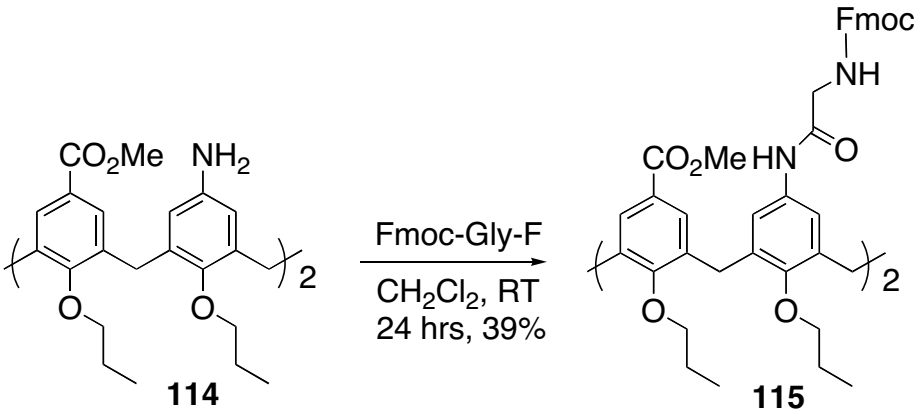

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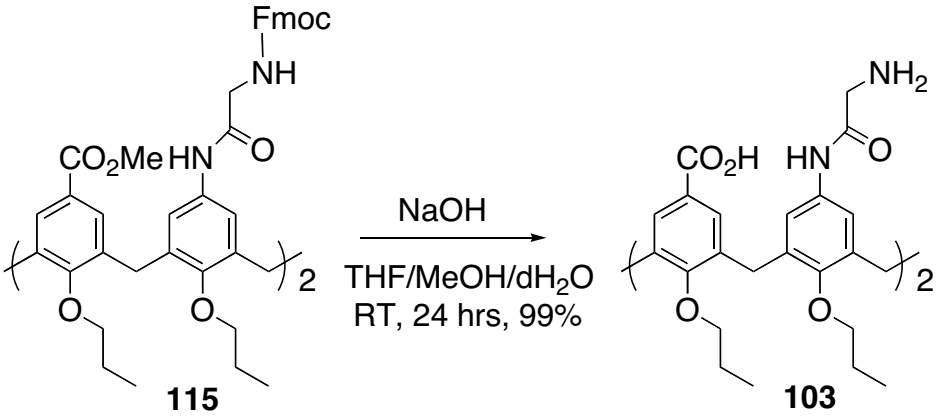

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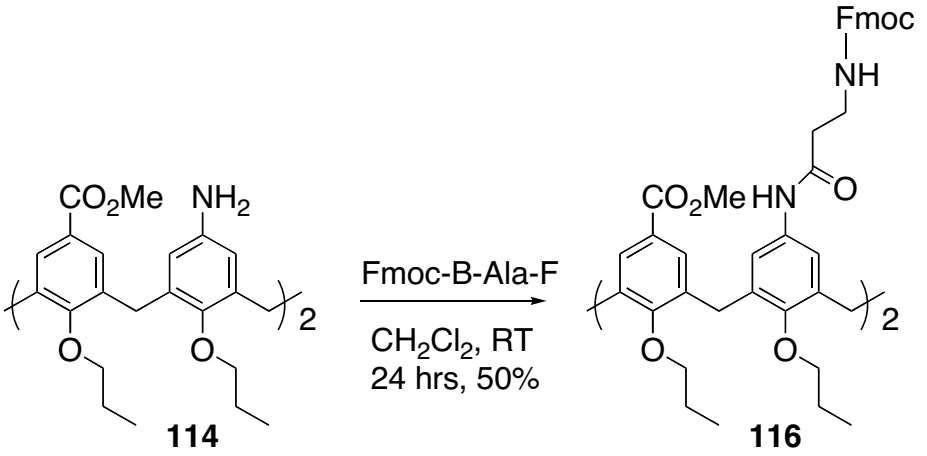
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2
O
O
114
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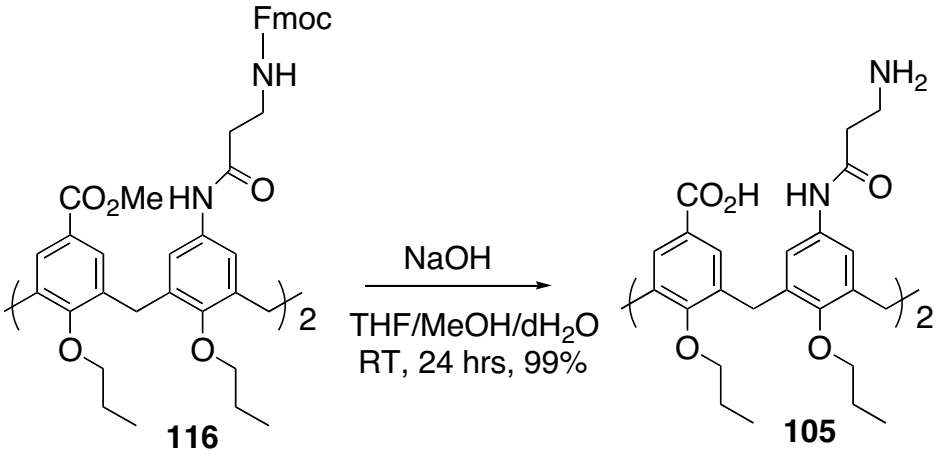
CH2Cl2, RT
24 hrs, 50%
Fmoc
NH
CO2Me
HN
O
116

150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NH2
CO2H
105

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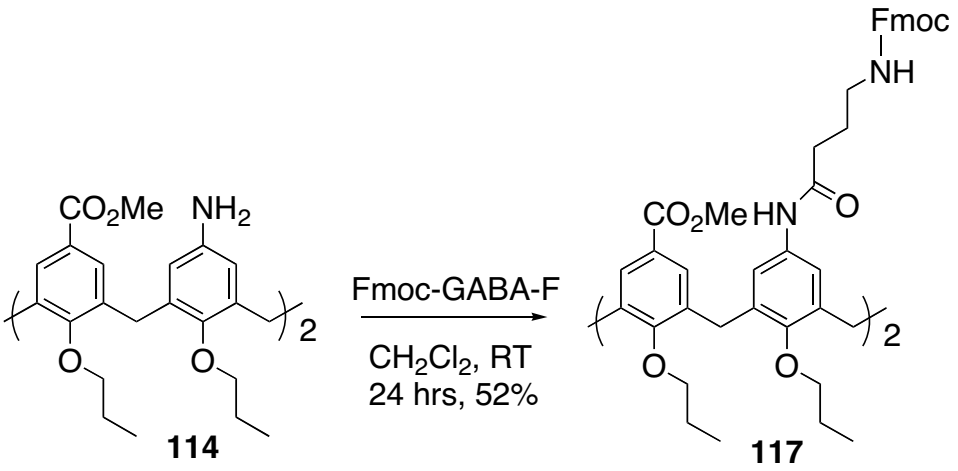
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HN
O
117

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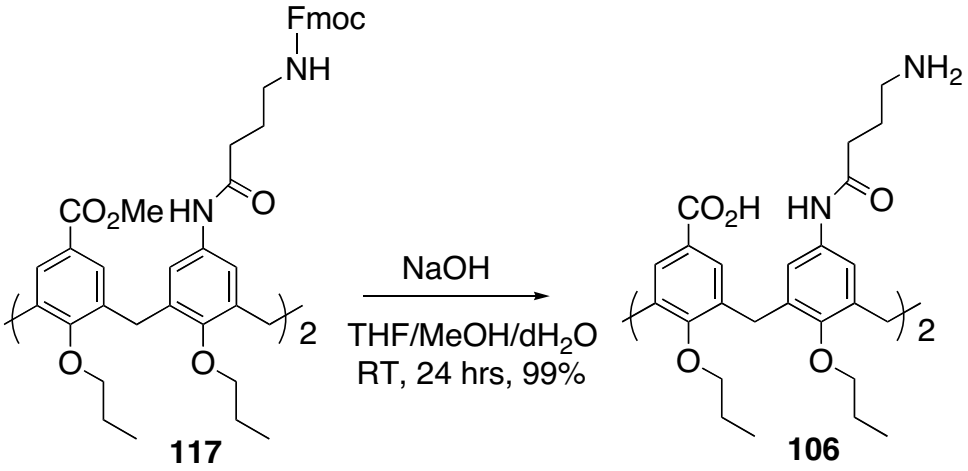

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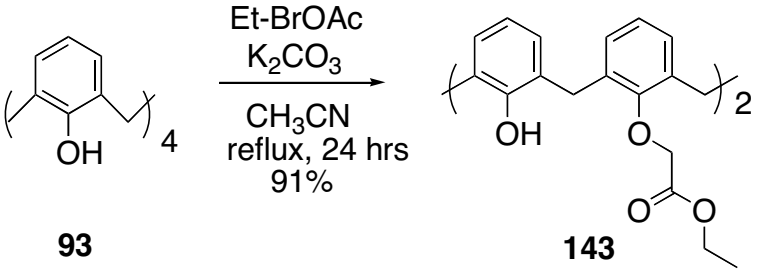

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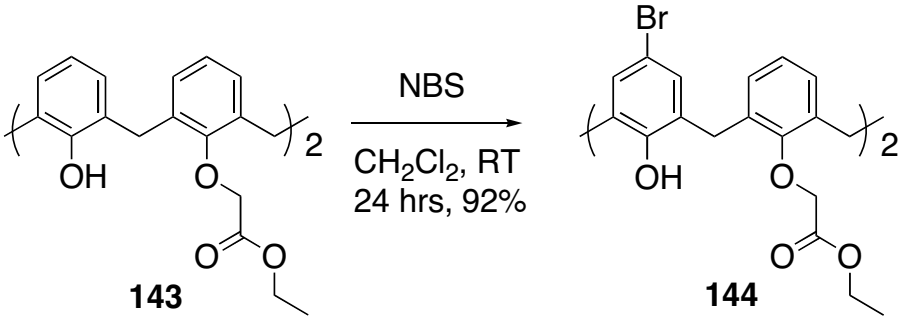

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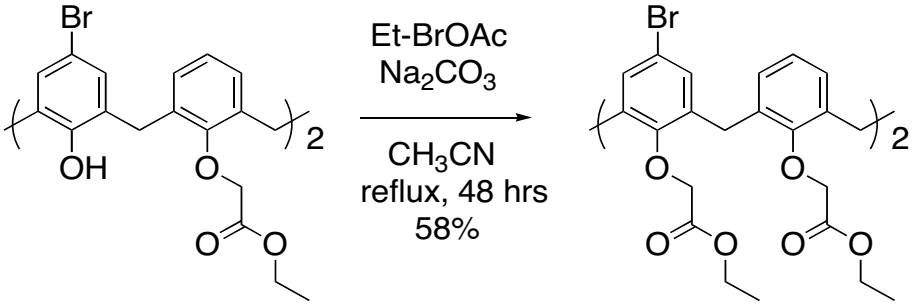
162



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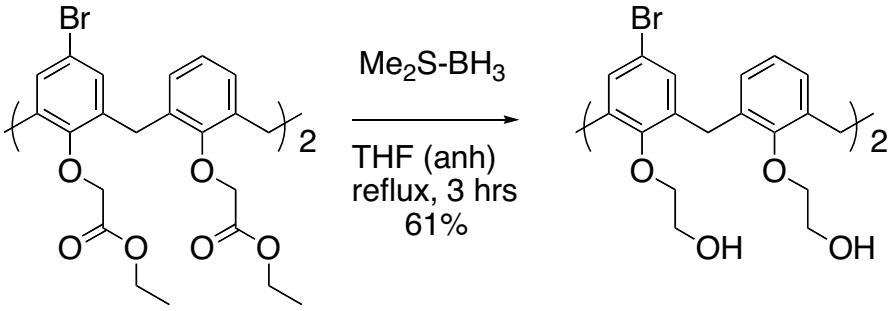
164



145 **141**

166

LIST OF SYMBOLS AND ABBREVIATIONS

AcOH	acetic acid
Ala	alanine
B-Ala	β-alanine
°C	degrees Centigrade
CD	Circular Dichroism
C-linked	linked through the carboxy terminus
DAST	(diethylamino)sulfer trifluoride
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ESI	electrospray ionization
Et-BrOAc	ethyl-bromoacetate
Et_3N	triethylamine
EtOH	ethanol
Fmoc	fluorenylmethoxycarbonyl
Fmoc-B-Ala-F	fluorenylmethoxycarbonyl-β-alanine acid fluoride
Fmoc-GABA-F	fluorenylmethoxycarbonyl-γ-amino butyric acid fluoride
Fmoc-Gly-F	fluorenylmethoxycarbonylglycine acid fluoride
g	gram
ΔG	the change in Gibbs Free Energy
GABA	γ-amino butyric acid
Gly	glycine
h, hr	hour
HRMS	High Resolution Mass Spectrometry

Hz	hertz
ITC	Isothermal Calorimetry
K	Kelvin
K_a	association constant
kcal	kilocalory
kJ	kilojoule
LAH	lithium aluminum hydride
m	*meta*
M	molar concentration
m-CPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
mg	milligram
mL	milliliter
mM	millimolar
mmol	millimole
mol	mole
*n*BuLi	*n*-butyl lithium
NBS	*N*-bromosuccinamide
N-linked	linked through the amino terminus
NMP	1-methylpyrrolidin-2-one
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
o	*ortho*
p	*para*

Ph	phenyl
ppm	parts per million
RT	room temperature
s	seconds
t-bu-Ala	*tert*-butyl-alanine
t-butyl	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

SUMMARY

Molecular capsules consist of two or more molecules that bind through either covalent or noncovalent interactions to form a structure with an internal void capable of containing guest molecules. These capsules can be used in catalysis/biocatalysis, in drug transport and delivery, in supramolecular arrays, and to stabilize reactive intermediates. Cavitands and calix[4]arenes are two types of macrocycles that have been used to form molecular capsules. Cavitands are used to form capsules called carceplexes, hemicarceplexes, and hemicarcerands through covalent bonds when two molecules are bridged together rim to rim. Calix[4]arene derivatives self-assemble reversibly through noncovalent interactions such as hydrogen bonding and ionic bonding to form capsules. Capsules formed form cavitands and calix[4]arenes have been shown to encapsulate a variety of guest molecules in nonpolar solvents. In order for the capsules to be used for biological applications, the capsules need to encapsulate guest molecules in water. There are only a few examples of capsules that encapsulate guests in polar solvents.

Calix[4]arenes derivatives substituted with charged substituents on the upper rim and propyl groups on the lower rim were synthesized. These derivatives dimerize through ionic interactions in polar solvents forming both heterodimers and homodimers. These dimers will be used to encapsulate various guest molecules. Although of the ionic propoxycalix[4]arene monomers are water-soluble, the dimers are not. This is due to the shielding of the charges upon assembly leaving only the propyl groups on the lower rim exposed to the polar solvent. To increase dimer solubility in water, calix[4]arene derivatives are being synthesized with hydroxy ethyl groups instead of the propyl groups

on the lower rim. When the charged hydroxyethoxycalix[4]arene derivatives dimerize, the alcohols will be exposed to the polar solvent instead of the propyl groups increasing the water-solubility.

CHAPTER 1

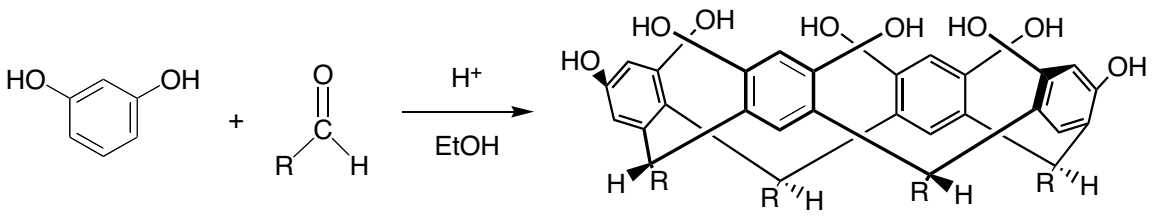
MOLECULAR CAPSULES

1.1 Molecular Capsules

Molecular capsules consist of two or more molecules that bind through either covalent or noncovalent interactions to form a structure with an internal void capable of containing guest molecules. These capsules can be used in catalysis/biocatalysis, in drug transport and delivery, in supramolecular arrays, and to stabilize reactive intermediates. Cavitands and calix[4]arenes are two types of macrocycles that have been used to form molecular capsules. Cavitands are used to form capsules called carceplexes, hemicarceplexes, and hemicarcerands through covalent bonds when two molecules are bridged together rim to rim. Calix[4]arene derivatives self-assemble reversibly through noncovalent interactions such as hydrogen bonding and ionic bonding to form capsules. Capsules formed form cavitands and calix[4]arenes have been shown to encapsulate a variety of guest molecules in various solvents.

1.2 Carceplexes, Hemicarceplexes, and Hemicarcerands

Cavitands are macrocyclic compounds composed of four resorcinols connected by methylenes that are synthesized by condensation of the resorcinols with aldehydes (Scheme 1-1).[1, 2] Cavitands are bowl shaped and contain cavities capable of binding small guest molecules.



Scheme 1-1. Synthesis of Cavitands

When an appropriate guest molecule is present in solution, cavitands self-assembly around the guest. These capsules can then be covalently linked rim-to-rim forming carceplexes and hemicarceplexes. Carceplexes are carcerands that contain a guest molecule that is encapsulated irreversibly when the carcerand is formed (Figure 1-1). Hemicarceplexes encapsulate guest molecules at ambient temperatures but release the guests at elevated temperatures (Figure 1-1).

Through molecular mechanics calculations, Houk *et al*. propose that "gates" control the encapsulation and release of guests in some hemicarcerands.[3] They proposed two types of gates, french doors and sliding doors. The French door gate opens and closes through chair-to-boat transitions of the methylenes of the cavitands. The sliding door gate opens and closes through conformational changes between the polar caps (cavitands) and the connecting bridges. The authors identified three types of host-guest carcerand complexes. The first type of complex, a carceplex, consists of a host with portals that are too small to allow guest entry or release. These complexes must be formed during synthesis of the carceplex and the guest is usually a solvent molecule. The second type of complex, a hemicarceplex, consists of a host with portals larger than the guests. In these complexes, guests move easily in and out of the host making it impossible to isolate and characterize the complex. The third and last type of complex, also a hemicarceplex,

contains portals that are smaller than the guests and do not allow passage into or out of the host until a conformational change occurs that opens the gate, increasing the size of the portal allowing the guest to enter or exit. Without gating, only molecules of similar size to the portal can enter the host and form a stable complex through constrictive binding.

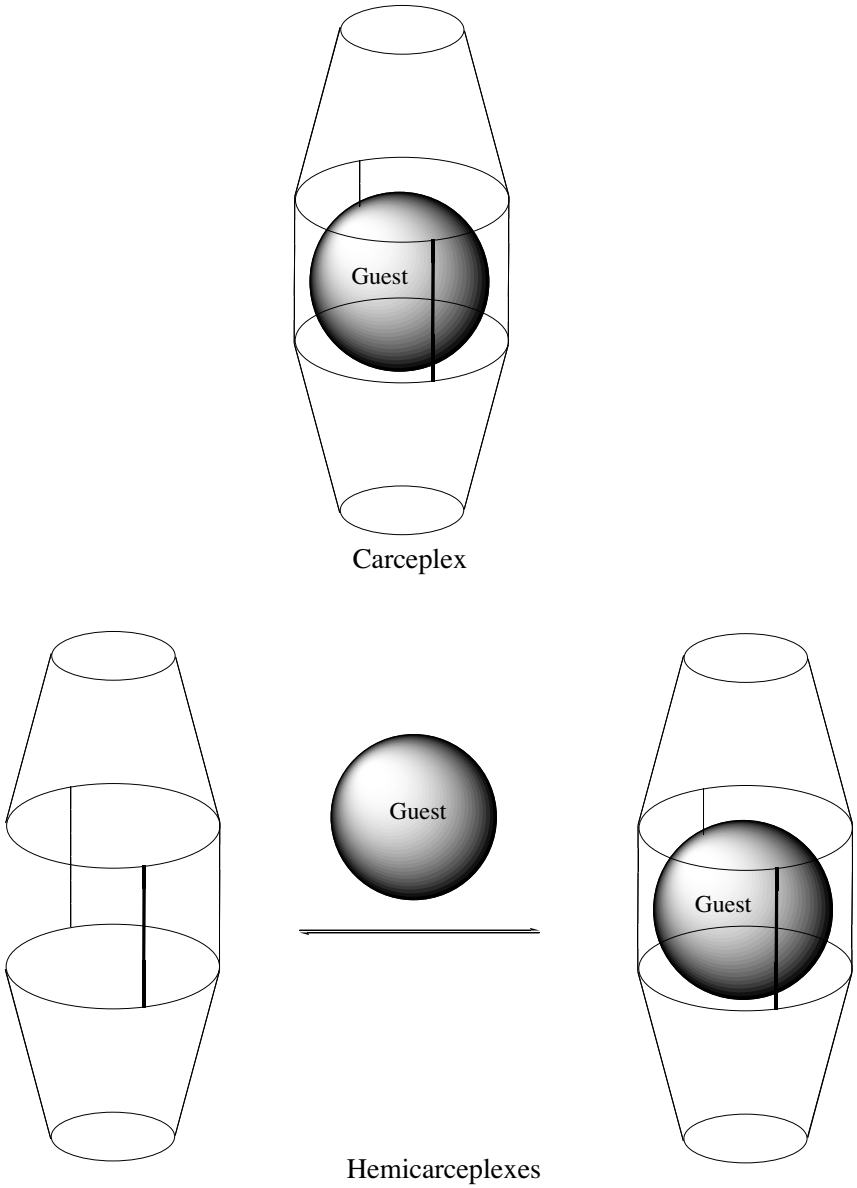
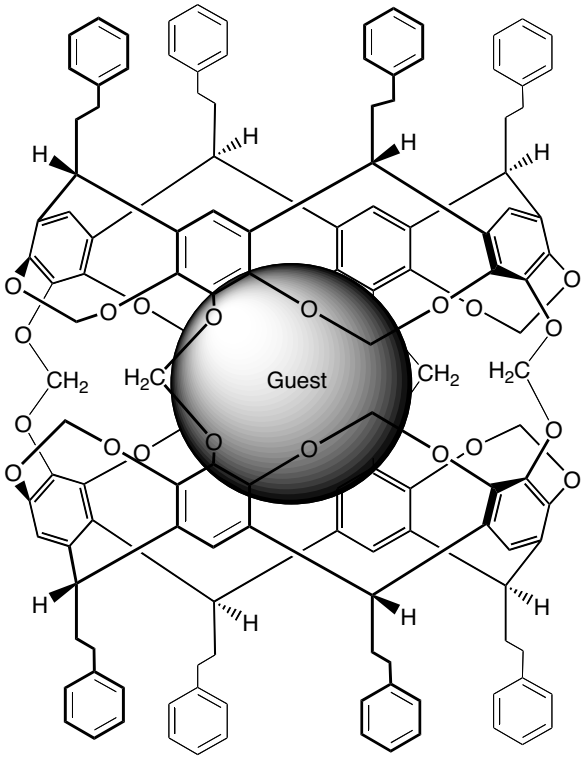


Figure 1-1. Carceplex and Hemicarceplex Structures

1.2.1 Carceplexes

Carceplexes consist of a hosts with portals that are too small to allow guest entry or release. These complexes must be formed during synthesis of the carceplex and the guest is usually a solvent molecule. Sherman and Cram[4] synthesized carceplexes that encapsulated one solvent molecule when the carcerand was synthesized. The synthesis of the carceplex required a guest of adequate size to act as a template and bring the two cavitand halves together so the bridges could be attached. Sherman *et al*.[5] used several molecules to probe the templating effects of the guest molecules on capsule formation. They found that carceplex **1** (Figure 1-2) is big enough to encapsulate molecules that are about seven nonhydrogen atoms in size.



1

Figure 1-2. Carceplex Structure

The largest and poorest guest that was encapsulated is 1-methylpyrrolidin-2-one. Competition experiments with various guests versus 1-methylpyrrolidin-2-one were carried out (Table 1-1). The capsule preferred guests with moderate polarity ranging from benzene to dimethyl sulfoxide (DMSO). Anything with either high (water) or low (cyclopentane) polarity was unsuitable as a guest for the carcerand synthesis. Symmetrical molecules were found to be better templates than nonsymmetrical molecules. Cyclic molecules were found to be better then acyclic molecules. No secondary amines were encapsulated. The guest with the best templating ability was pyrazine.

Table 1-1. Carceplex Yields and Competition Experiments

guest	yield (%)[a]	ratio[b]	conditions[b]
pyrazine	87	1000000	A
1,4-dioxane	68	290000	A
dimethyl sulfide	52	180000	A
dimethyl sulfoxide	63	70000	A
1,3-dioxolane	64	38000	A
2-butanone	75	37000	A
pyridine	46	34000	A
dimethyl sulfone	60	19000	A
furan	54	12000	A
tetrahydrofuran	50	12000	A
acetone	51	6700	A
thiophene	23	5800	A
benzene	43	2400	A
2-propanol	74	1500	A
pyrrole	73	1000	B
tetrahydrothiophene	34	410	B
1,3-dioxane	45	200	B
acetamide	26	160	B
trioxane	24	100	B
acetonitrile	35	73	B
ethanol	38	61	B
dimethylacetamide	15	20	B
dimethylformamide	4	7	B
NMP	5[c]	1	B

[a]Yield refers to the reaction run with one guest only. [b]A: 1 mol% guest. B: 5 mol% guest, 1 day at 25 °C, 2 days at 60 °C. [c]Reaction was run in 100% NMP.

1.2.2 Hemicarcerands and Hemicarceplexes

Hemicarceplexes contain portals that are smaller than the guests and do not allow passage into or out of the host until a conformational change occurs that increases the size of the portal allowing the guest to enter or exit. The synthesis and study of various different hemicarcerands is an ongoing project for Dr. Donald Cram and his research group. They have synthesized several hemicarcerands containing different bridging linkers (Figure 1-3). The first hemicarcerand synthesized **(2)** was connected by three methylene bridges and was studied for its ability to encapsulate and release various guests.[6] The term constrictive binding was used to define the energy barrier from the opening and stretching of the portal that must be overcome for a guest to enter or exit the capsule. This barrier leads to stable hemicarcerands/hemicarceplexes that do not allow guests to enter or leave the capsule at room temperature but do allow guest entry or release at elevated temperatures. Hemicarcerand **2** was found to bind N_2, O_2, H_2O, and CO_2 at room temperature with free energies of –2 to –3 kcal/mol but the hemicarceplexes were not isolatable. Compound **2** was able to encapsulate CS_2, Xe, CH_3CN, CH_2Cl_2, CH_2Br_2, and CS_2 in solution at room temperature and the hemicarceplexes were isolated and characterized. When **2** was heated in large solvents, such as pyridine, benzene, tetrahydrofuran (THF), diethylamine, or butylamine, one solvent molecule was encapsulated.

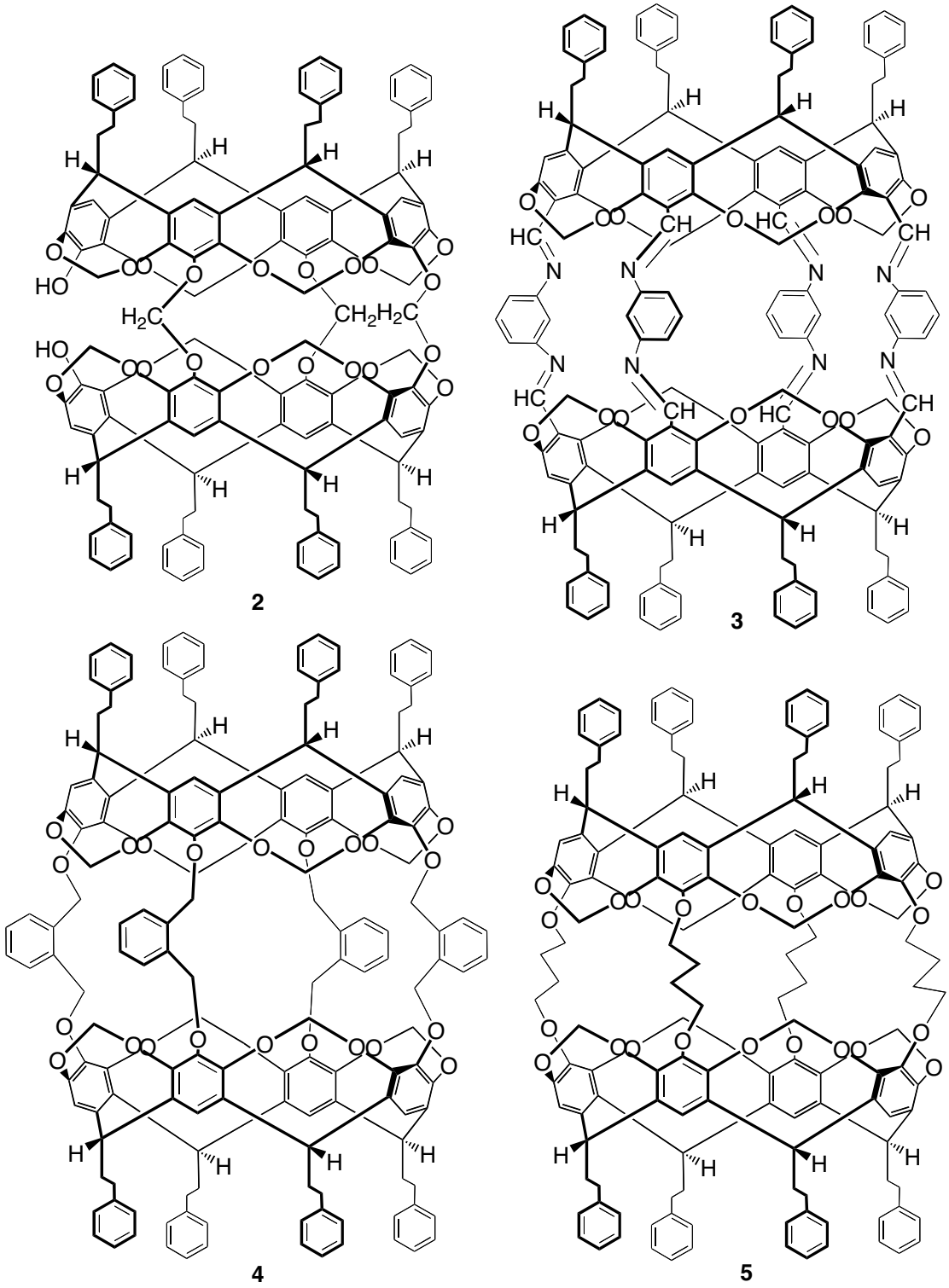


Figure 1-3. Hemicarcerand Structures

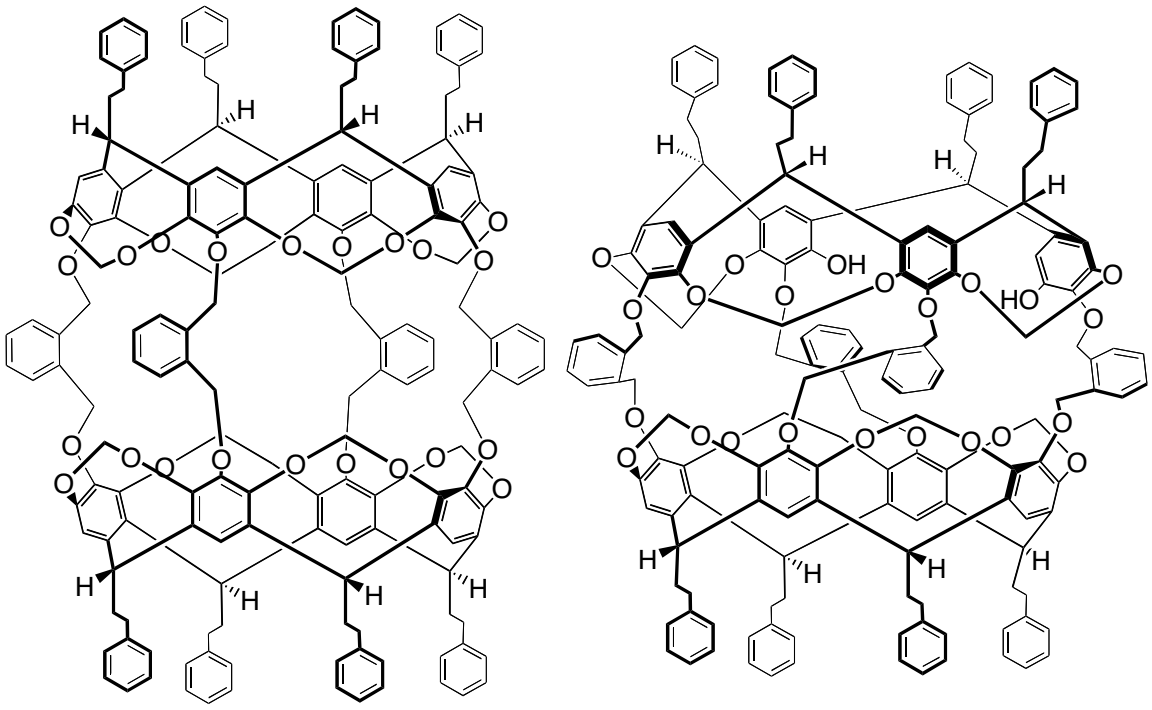
Four rigid 1,3-di(methylimide)benzene spacers were used to synthesize a larger hemicarcerand **3** (Figure 1-3).[7] It was found to encapsulate large guest molecules such as hexachlorobutadiene, triethyl phosphate, tripropyl phosphate, menthol, anthraquinone, hexamethylphosphoramide, anthracene, camphor, ferrocene, ruthenocene, amantadine, hexamethylenetetramine, adamantane, and [2.2]paracyclophane at elevated temperatures. All of these hemicarceplexes were isolatable and characterizable at room temperature.

1,3-Dimethylbenzene connecting bridges were used to synthesize hemicarcerand **4** that was more flexible then the rigid 1,3-di(methylimide)benzene bridged hemicarcerand **3** (Figure 1-3).[8] Compound **4** was found to exist in two forms, open and closed (Figure 1-4). In the open form, the polar caps are symmetrically aligned with one another and the portal is opened wide enough to allow entry and release of guest molecules. In the closed form, one polar cap is rotated 21 ° compared to the other. This rotation brings the polar caps closer together and shrinks the size of the portal locking in any guest molecules. The hemicarcerand was found to adopt the closed form at room temperature but the energy barrier required for the hemicarcerand to untwist and open was overcome at elevated temperatures (~100 °C). Several guests were encapsulated at elevated temperatures such as ethylbenzene, 1,4-dimethylbenzene, tetrachloroethane, dimethylaminomethylketone, dimethylformamide (DMF), acetonitrile, 1-butanol, ethylmethylketone, ethylacetate, THF, toluene, and chloroform. The decomplexation rates and half-life's for these complexes are listed in Table 1-2. Interestingly, both the shape and size of the guest influenced encapsulation. For example, *p*-Xylene was encapsulated but *m*-xylene and *o*-xylene were not.

Table 1-2. Dependence of Decomplexation Rates on Guest Structure of **4**:Guest in $CDCl_2$ at 100 °C

guest	$t_{1/2}$ (min)	k_1 (s^{-1} x 10^4)
acetonitrile	38	3.0
dimethylformamide	42	2.7
dimethylaminomethylketone	45	2.6
tetrahydrofuran	87	1.3
toluene	209	0.55
1-butanol	260	0.44
ethylmethylketone	308	0.39
tetrachloroethane	352	0.33
ethyl acetate[a]	409	0.28

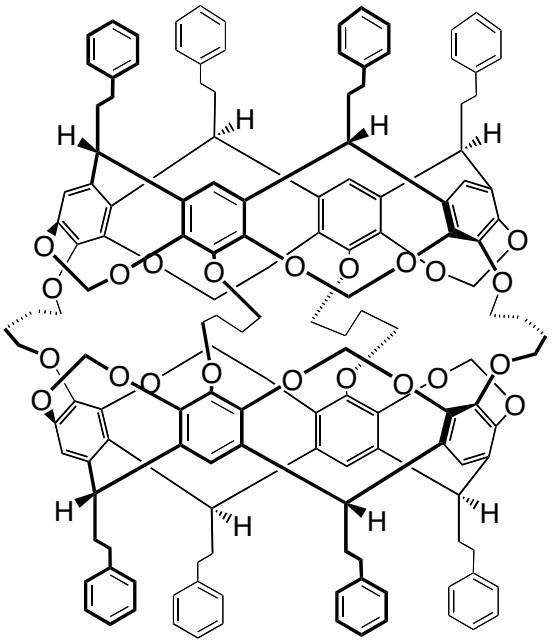
[a]Estimated from rate constant at 130 °C assuming it decreased by a factor of 3 in going to 100 °C, as was observed in $(CD_3)_2C_6D_4$ as solvent.



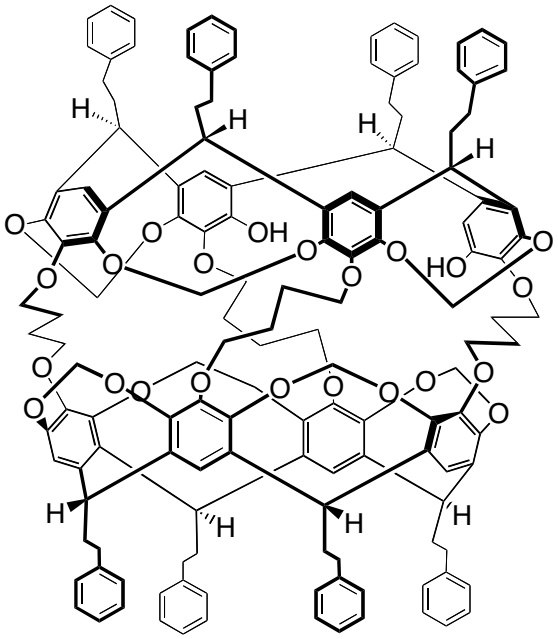
Untwisted-Open Form Twisted-Closed Form

Figure 1-4. Dimethylbenzene Bridged Hemicarcerands

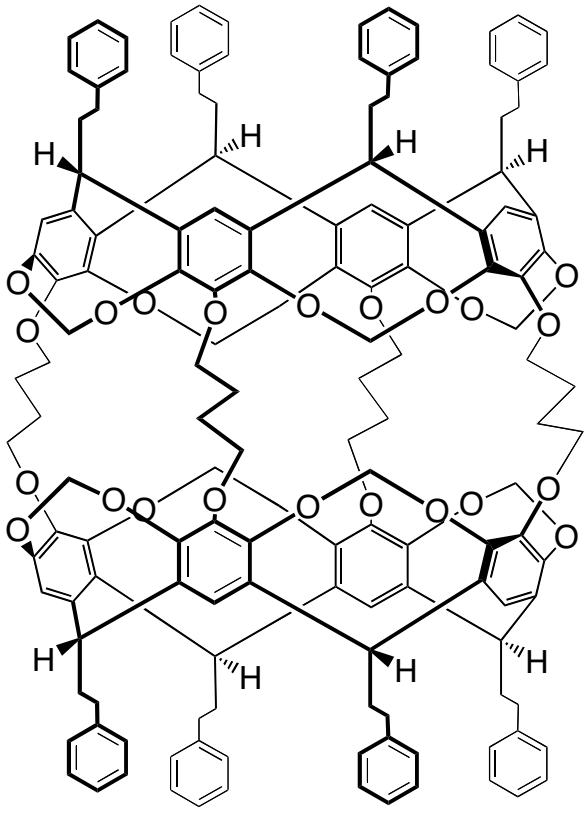
Hemicarcerand **5** (Figure 1-3), containing four butane connecting bridges, was synthesized by Cram *et al*.[9] The more flexible butane derivative was found to bind a wider variety of guests, and bound them tighter than the 1,3-dimethylbenzene derivative **(4)**. Compound **5** was found to bind guests of various sizes ranging from Xe to iodoethane to disubstituted toluenes. Similar to hemicarcerand **4**, **5** was found to adopt three different conformations: untwisted-open, untwisted-closed, and twisted-closed. In the first conformation, the lone pairs on the eight oxygen atoms connected to the bridges point outward and the bridges point inward. The second conformation is the opposite with the lone pair pointing in and the bridges pointing out. In this conformation, the two polar caps can twist about 15 ° with regard to each other. As seen before, this pulls the polar caps closer together and shrinks the portal and cavity size. The shape and alignment of the guest greatly influences the ability of the hemicarcerand to twist. The nonsymmetric acyclic compounds and the more substituted aromatic compounds prevent twisting of the polar caps. When twisting was prevented by the guest, the host was still able to minimize the cavity size by rotating the butane bridges perpendicular to the plane of the polar axis bringing the polar caps closer together (Figure 1-5).



Untwisted-Closed



Twisted-Closed



Untwisted-Open

Figure 1-5. Butane Bridged Hemicarcerands

Hemicarcerands containing large portals were also synthesized.[10] These hemicarcerands contained either four 2,4-hex-diyne connecting bridges **(6)** or four hexane connecting bridges **(7)** (Figure 1-6). The triple bonds of the 2,4-hex-diyne hemicarcerand were reduced to form the hexane bridged hemicarcerand, which could not be synthesized directly due to the intramolecular reaction of the linker with the adjacent hydroxyls. Compound **6** was found to encapsulate hydrocarbons with molecular weights up to 236 g/mol such as 1,3,5-triethylbenzene, 1,3-dimethyladamantane, [3.3]paracyclophane, 4-ethyl[2.2[paracyclophane, and three disubstituted [2.2]paracyclophanes. Encapsulation studies on the more flexible hexane bridged hemicarcerand have not been completed.

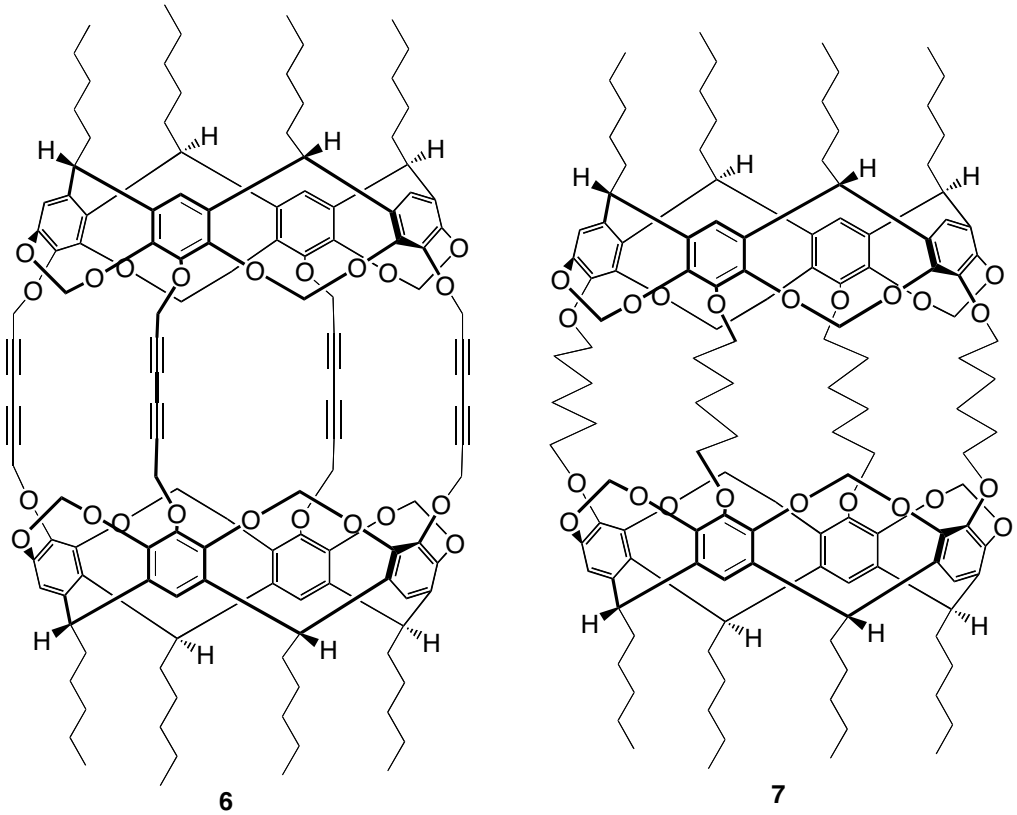


Figure 1-6. Large Portal Hemicarcerands

1.2.3 Asymmetric and Water-Soluble Hemicarcerands and Hemicarceplexes

Two asymmetric hemicarcerands containing three butane connecting bridges and one chiral connecting bridge have been synthesized.[11] One of the chiral bridges is an acetonide ring **(8)** and the other is a 2,2'-bisoxymethylene-1,1'-binapthyl moiety **(9)** (Figure 1-7). These hemicarcerands were studied for their ability to selectively bind chiral guests. The binapthyl bridged hemicarcerand **(9)** was able to bind only one guest, (*R*)-4-methyl-*p*-tolylsulfoxide, with high selectivity (>20:1). Other guests were encapsulated with ratios ranging from 2.7:1 to 1:1. The acetonide bridged hemicarcerand was found to have lower selectivity than the binapthyl bridged capsule.

In order to be used in biological systems, water-soluble capsules are needed. Hemicarcerand **10a** containing four 3,5-dimethyl-2,6-dicarboxylicacidbenzene connecting bridges was synthesized (Figure 1-7).[12] This octaacid hemicarcerand was found to be water soluble and to encapsulate several guest molecules in D_2O at pH 9. Additionally, **10a** was able to bind 1,4-dimethylbenzene and 1,4-dimethoxybenzene better in D_2O than the non water-soluble benzyl bridged hemicarcerand **10b** in $CDCl_3$. Hemicarcerand **10a** was not able to encapsulate lipophilic salts such as tetramethylammonium bromide, trimethylphenylammonium bromide, trimethylbenzylammonium bromide, and sodium 3-methylbenzoate. The authors rationalize that the D_2O was able to solvate the salts better than the interior of the capsule.

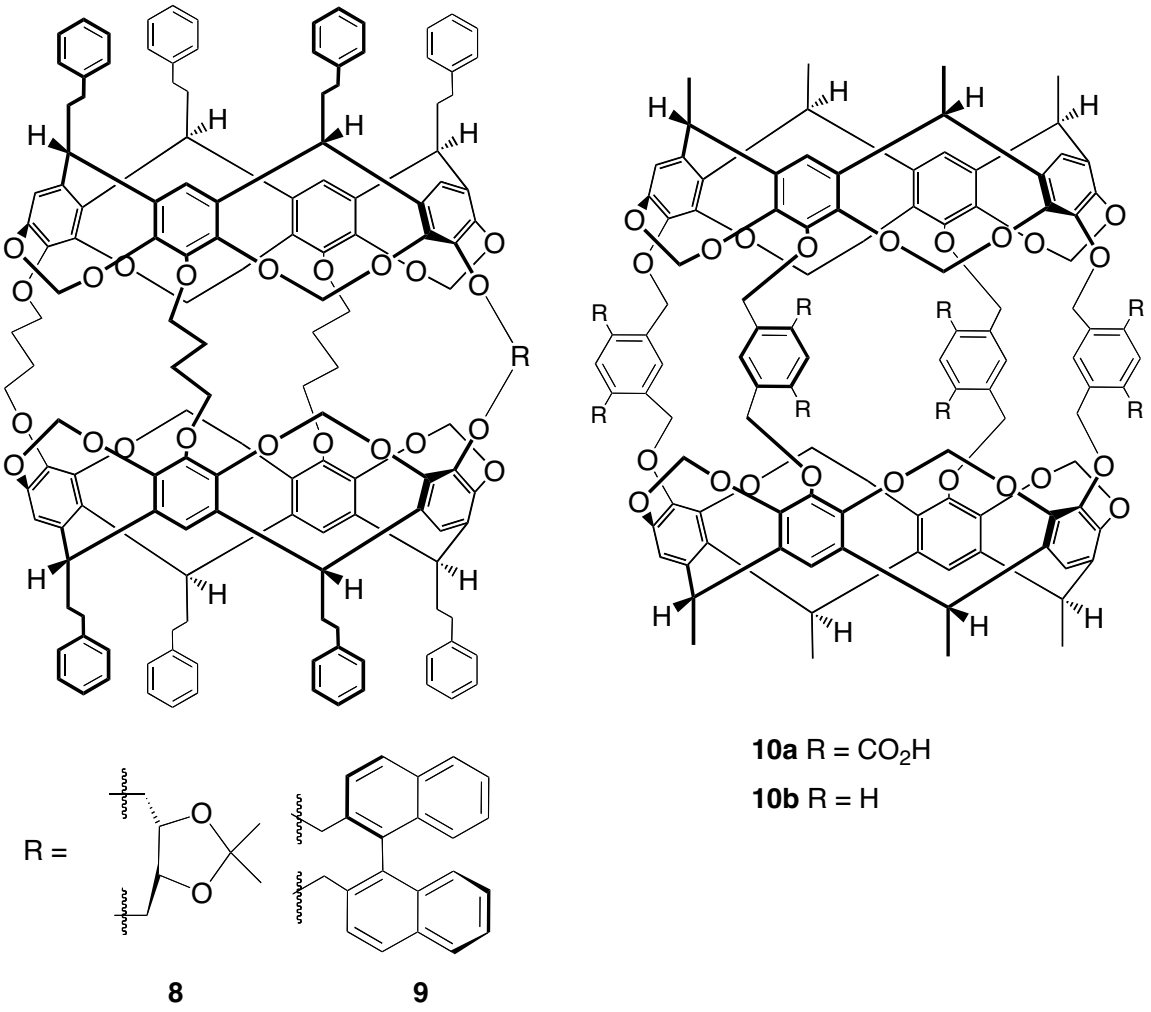


Figure 1-7. Asymmetric and Water-Soluble Hemicarcerands

1.2.4 Reactions within Hemicarceplexes

One application of hemicarceplexes is the stabilization and protection of reactive guests synthesized within the capsule. Cyclobutadiene is a very reactive molecule that was synthesized within hemicarcerand **2** from α-pyrone.[13] α-Pyrone was encapsulated in **2** where it was photochemically converted into photopyrone. Upon further irradiation, the photopyrone was converted into cyclobutadiene (Figure 1-8). The encapsulated cyclobutadiene was stable in deoxygenated solution up to 60 °C. Previously,

cyclobutadiene had only been studied in cryogenic matrices below 8 K.[14] With further irradiation, the encapsulated cyclobutadiene decomposed into acetylene that easily escaped the capsule. When the encapsulated cyclobutadiene was heated to 220 °C in THF, cyclobutadiene was released into the solvent and dimerized to produce cyclooctatetra-1,3,5,7-ene. Additionally, encapsulated cyclobutadiene was found to react inside the capsule with oxygen from the solution forming maleic anhydride.

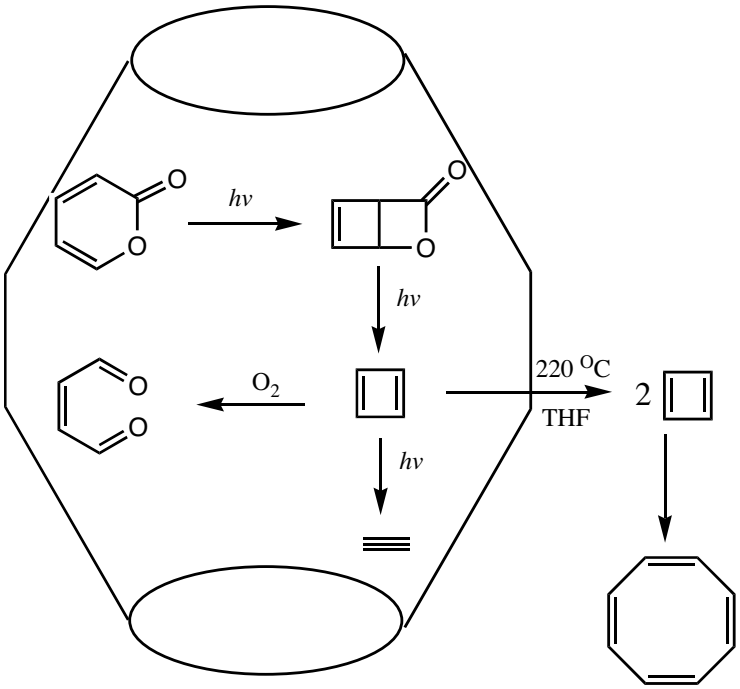
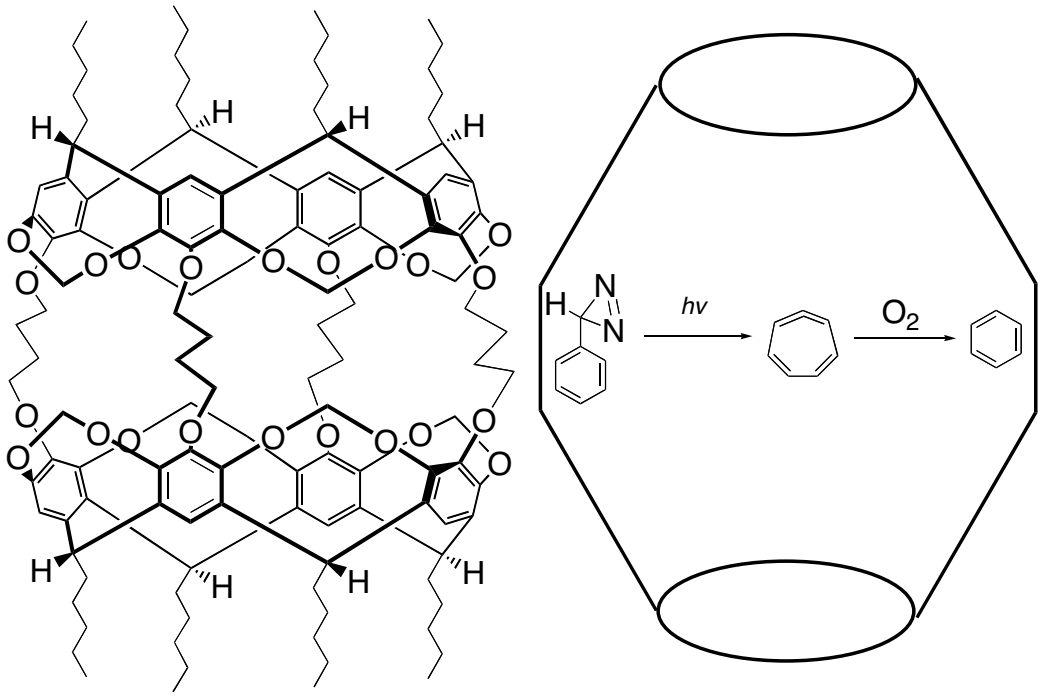


Figure 1-8. Synthesis and Reactions of Cyclobutadiene in Hemicarcerand **2**

1,2,4,6-cycloheptatetraene is a highly reactive molecule that has been stabilized by encapsulation within a hemicarcerand.[15] Phenyldiazirine was encapsulated in hemicarcerand **11.** Cycloheptatetraene was synthesized through a photochemical phenylcarbene rearrangement of the encapsulated phenyldiazirine and is stable for weeks at room temperature in solution without oxygen (Figure 1-9). Although unreactive

towards water and methanol even at 60 °C, the addition of oxygen to the solution converts the cycloheptatetraene into benzene. The free cycloheptatetraene reacts rapidly with both water and methanol.



11

Figure 1-9. Synthesis of 1,2,4,6-Cycloheptatetraene in Hemicarcerand **11**

Hemicarcerand **5** containing four butane bridges was also used to stabilize reactive guests[16] and as a container for through shell reactions.[17, 18] *o*-Benzyne, another highly reactive molecule, was previously only studied in cryogenic conditions bellow 77 K. Warmuth encapsulated benzocyclobutenedione in **5**.[16] The encapsulated benzocyclobutaenedione was photochemically converted ($\lambda > 400$ nm) into benzocyclopropenone at 77 K. The encapsulated benzocyclopropenone was stable at room temperature for several days, and could also be photochemically converted ($\lambda < 297$

nm) into *o*-benzyne at 77 K (Figure 1-10). When the *o*-benzyne hemicarcerand complex was heated from 77 K to –75 °C, the *o*-benzyne reacted through a Diels-Alder reaction with one of the benzene rings of the hemicarceplex.

Cram *et al*. studied the oxidation and reduction of encapsulated hydroquinones and quinones (Figure 1-10) in **5**.[17] Several quinones were synthesized from the encapsulated hydroquinones in quantitative yields. These quinones could not be encapsulated due to their instability in solution at elevated temperatures and had to be synthesized inside the capsules. The quinones were stable in the capsules up to 100 °C. The quinones could also be reduced back to the hydroquinones quantitatively. Interestingly, nitrobenzene encapsulated in **5** was reduced to *N*-hydroxyaniline with samarium iodide and methanol in THF. Under the same conditions, free nitrobenzene is reduced to aniline. Hemicarcerand **5** was also used to study the alkylation of various hydroxy substituted benzenes.[18] The authors found that guest orientation and reagent size played a big part in the alkylation. The guests usually oriented themselves in the capsule with at least one of the substituents in the polar cap. Guests, such as 2-hydroxytoluene, 3-hydroxytoluene, and 1,3-hydroxybenzene, that contained equatorially located hydroxyls could be methylated, but guests that contained *para* substituents were not methylated because both substituents were located in the polar caps. 1,2-Hydroxybenzene oriented itself with one hydroxyl in the polar cap and the 0other in the equatorial region allowing monomethylation to occur but not dimethylation.

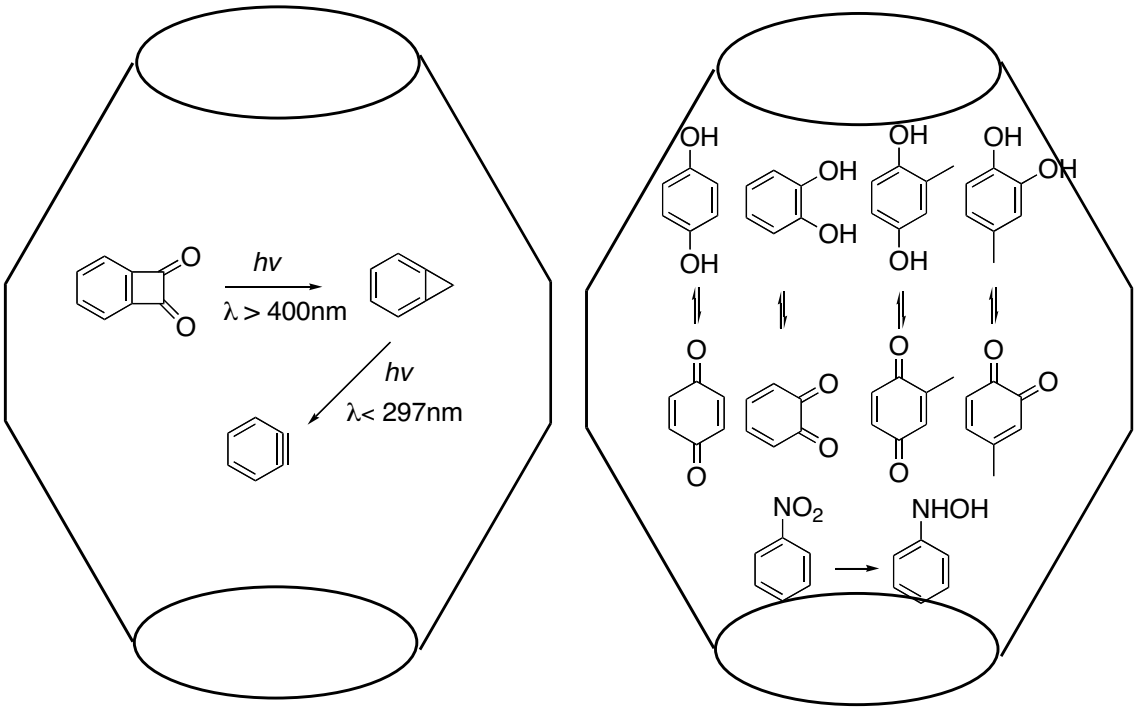
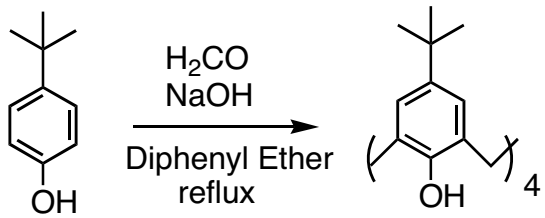


Figure 1-10. Reactions in Hemicarcerand **5**

1.3 Calix[4]arenes

Calix[4]arenes are macrocycles composed of four phenols connected through their *ortho* positions by methylene bridges. They are synthesized by condensation of *t*-butylphenol and formaldehyde (Scheme 1-2).[19]



Scheme 1-2. Calix[4]arene Synthesis

Calix[4]arenes exist in four different interconverting conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate (Figure 1-11).[20] The conformations interconvert by rotation of one phenol hydroxyl through the annulus of the macrocycle.

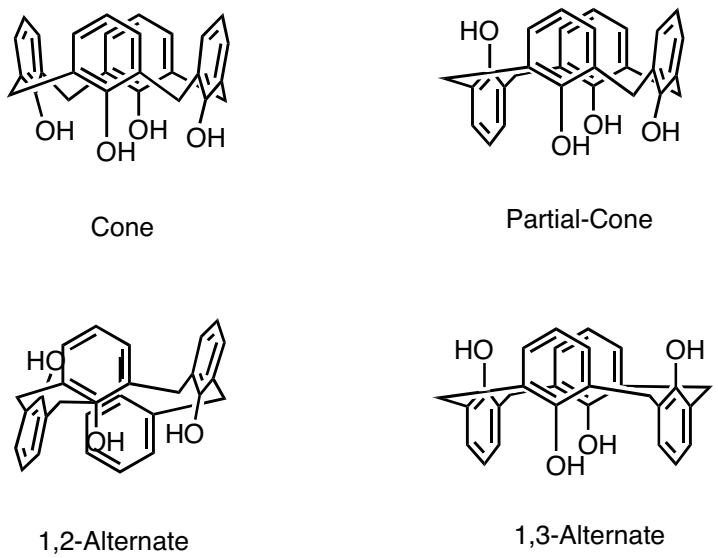


Figure 1-11. Calix[4]arene Conformations

The cone conformation is the most stable due to intramolecular hydrogen bonding of the phenolic hydroxyls. Alkylating the phenolic oxygen, or lower rim, with either a propyl group or a larger functional group prevents the calix[4]arene from interconverting between conformations and is easily achieved through a Williamson ether synthesis. The cone conformation is bowl shaped and contains a cavity capable of binding small guest molecules (Figure 1-12). By functionalizing the upper rim, calix[4]arene derivatives, that self-assemble through hydrogen or ionic bonding to form molecular capsules, can be synthesized. Upon assembly, these capsules can reversibly encapsulate guest molecules within the interior of the capsule (Figure 1-13).

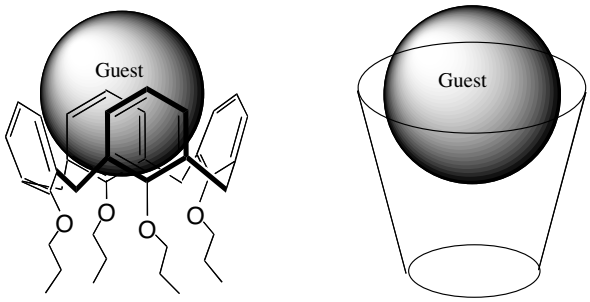


Figure 1-12. Calix[4]arene Cone Conformation

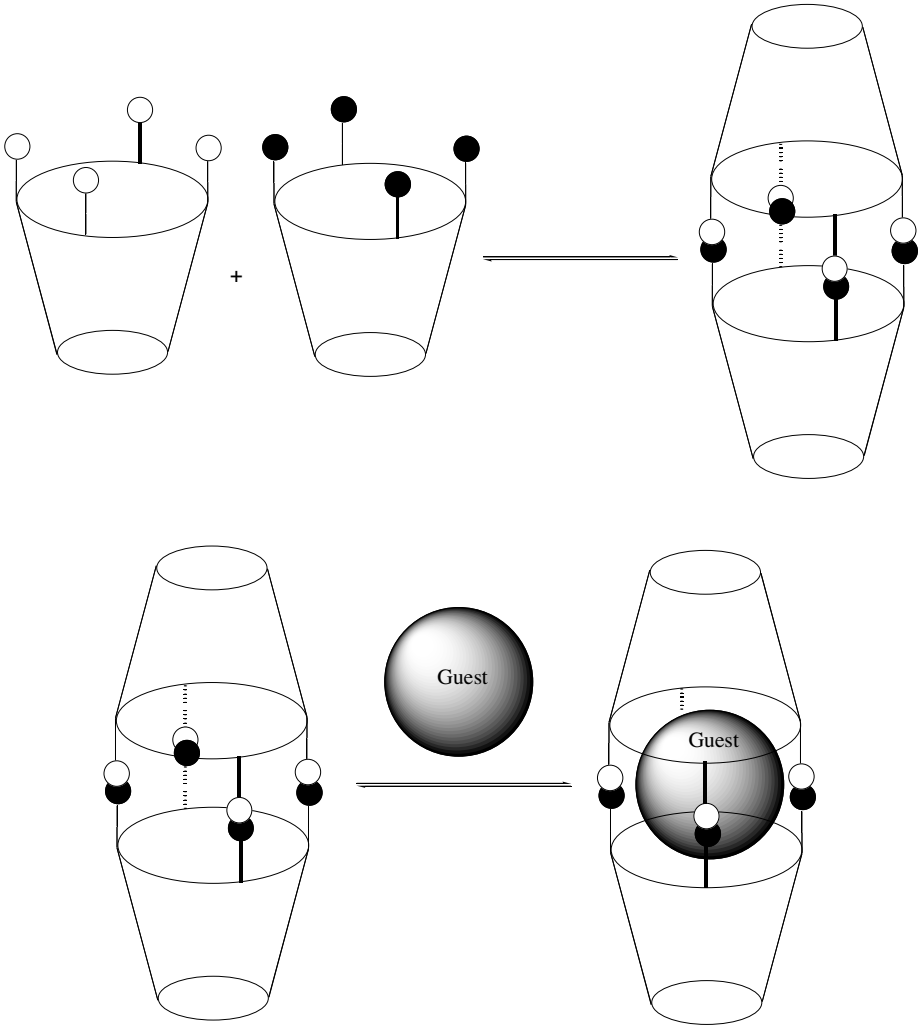
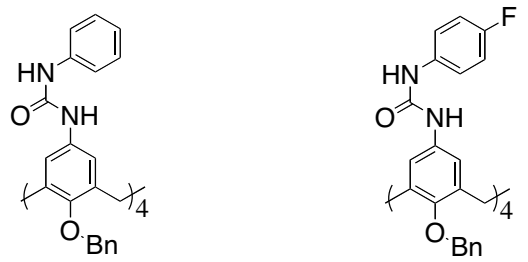


Figure 1-13. Calix[4]arene Self-Assembly and Encapsulation

1.3.1 Hydrogen Bonded Capsules in Nonpolar Solvents

Several calix[4]arene derivatives that self-assemble through hydrogen bonding to form capsules in nonpolar solvents have been developed. Shimizu and Rebek synthesized a phenylurea functionalized calix[4]arene derivative substituted on the lower rim with benzyl groups **(12)** (Figure 1-14).[21] ^{1}H NMR studies showed that **12** self-assembled into a homodimer **(12:12)** in nonpolar solvents such as chloroform. The ^{1}H NMR spectrum of the capsule was symmetric and well resolved, which is consistent with dimer formation. Due to the symmetry of the ^{1}H NMR spectrum, it was deduced that the capsule must be asymmetric with all of the ureas oriented in the same direction. The ^{1}H NMR spectrum also showed a high degree of hydrogen bonding. The urea protons were shifted downfield compared to the urea protons in the spectrum of the monomer. The addition of a polar solvent, such as DMSO, disrupts the hydrogen bonding causing the capsule to dissociate into its monomers. ^{1}H NMR studies showed that the homodimer was able to encapsulate several different solvents. Competition experiments were performed with homodimer **12:12** and equimolar mixtures of the guests. The relative populations of homodimer:guest complexes were compared and benzene and chloroform were found to be the best guests followed by toluene, *o*-xylene, *p*-xylene, and ethyl benzene. The encapsulation of the guests is size dependent with the smaller guests being bound more tightly. Both *ortho*-xylene, *para*-xylene, and ethylbenzene are similar in size but the capsule prefered *o*-xylene due to guest shape instead of guest size. Encapsulation was also seen in the gas phase. Peaks for the complexes of the capsule with benzene, chloroform and methylene chloride were seen by MS, but peaks for the complexes with larger guests such as ethylbenzene and xylene were not.



12 **13**

Figure 1-14. Phenylurea- and Fluorophenylureacalix[4]arenes

A calix[4]arene derivative **(13)** with fluorophenylureas on the upper rim was studied for its ability to encapsulate guest molecules (Figure 1-14), using ^{19}F and ^{1}H NMR.[22] Fluorophenylurea was used so that the fluorine atoms could act as an internal standard for the ^{19}F spectroscopy studies. Calix[4]arene **13** was seen to form a homodimer in nonpolar solvents but dissociated upon addition of small amounts of polar solvents, much like the phenylurea derivative. Addition of fluorobenzene to a solution of the homodimer in *p*-xylene-d_{10}, caused a signal to appear upfield in the ^{19}F NMR that corresponded to the encapsulated fluorobenzene. Integration of the signals shows a 1:1 ratio of capsule to guest. In the ^{1}H NMR spectrum, different peaks are seen for the *ortho, meta,* and *para* protons of the fluorobenzene with the *para* protons being more than 2 ppm away from the *ortho* protons. This is consistent with the fluorobenzene being oriented with the fluorine and *para* proton pointing at the ureas and the *ortho* and *meta* protons being pointed towards the phenyl rings. Addition of phenyl-α-phenylethyl urea to the solution breaks up the complex and releases the guest due to competitive hydrogen bonding between the phenyl-α-phenylethyl and the calix[4]arene. Other guests were also

encapsulated including benzene, *p*-difluorobenzene, chlorobenzene, toluene, phenol, aniline, pyrazine, and pyridine. Benzene was found to have an association constant of 230 M^{-1}. The relative affinities of the guests compared to that of benzene are listed in Table 1-3.

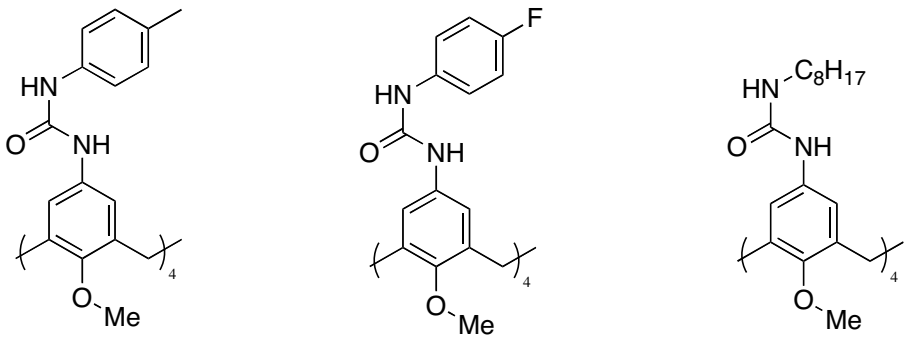
Table 1-3. Relative Affinities of **13:13** for Guests in Competition with Benzene[a]

	Affinity	
Guest	T = 25 °C	T = 50 °C
C_6H_6	1.0	0.82
C_6H_5F	2.6	2.5
p-$C_6H_4F_2$	5.8	6.9
C_6H_5Cl	0.30	0.55
$C_6H_5CH_3$	<0.1	<0.1
C_6H_5OH	0.83	1.2[b]
$C_6H_5NH_2$	0.32	0.39
pyrazine	3.2	3.0
pyridine	1.2	1.1

[a]Concentration of dimer is 2.936 x 10^{-3} M; guest and benzene concentrations are 21.94 x 10^{-3} M each. [b]A precipitate formed after several hours.

More flexible calix[4]arene derivatives (Figure 1-15) with methoxy groups on the lower rim and substituted ureas on the upper rim have also been synthesized.[23] The ureas were substituted with toluene **(14)**, fluorobenzene **(15)**, or octane **(16)**. The methoxy groups on the lower rim are not large enough to lock the derivative in a single conformation, making the derivatives more flexible then the previous examples **12** and **13**. Each derivative exists in all of the conformations with the partial cone conformation (96%) being the most favorable. For all of the dimers studied, the energy gained from the formation of 16 hydrogen bonds during dimerization was high enough to overcome the energy barrier needed (~13 kcal) for the derivative in the partial cone form to convert into the cone form. Derivatives **14** and **16** were combined in a 50/50 ratio and studied by ^1H

NMR. The ^{1}H NMR spectrum revealed peaks for three different dimers, two homodimers **14:14**, **16:16**, and one heterodimer **14:16**. These dimers were found to encapsulate benzene.



14 **15** **16**

Figure 1-15. Flexible Ureacalix[4]arene Derivatives

Extended calix[4]arene derivatives **17** and **18** with substituted ureas attached to phenyl spacers on the upper rim were synthesized by Rebek *et al*.[24] The extended calix[4]arene derivatives were found to form homodimer **17:17**, homodimer **18:18**, and heterodimer **17:18** in chloroform-*d* and methylene chloride-d_2. The homodimer **18:18** was studied for the encapsulation of several different guests (Figure 1-16). The extra phenyl spacers created large pores in the capsule that allowed solvent molecules to enter and exit rapidly. No encapsulation was seen for the neutral guests **(24-26)** but, encapsulation was observed for the cationic guests **(19-23)**. The guest exchange was fast on the NMR time scale so only a complex induced shift in the guests ^{1}H NMR signals was seen. The association constant for guest **19** in methylene chloride-d_2 was calculated to be between 5.6 x 10^3 and 1.9 x 10^5 M^{-1}.

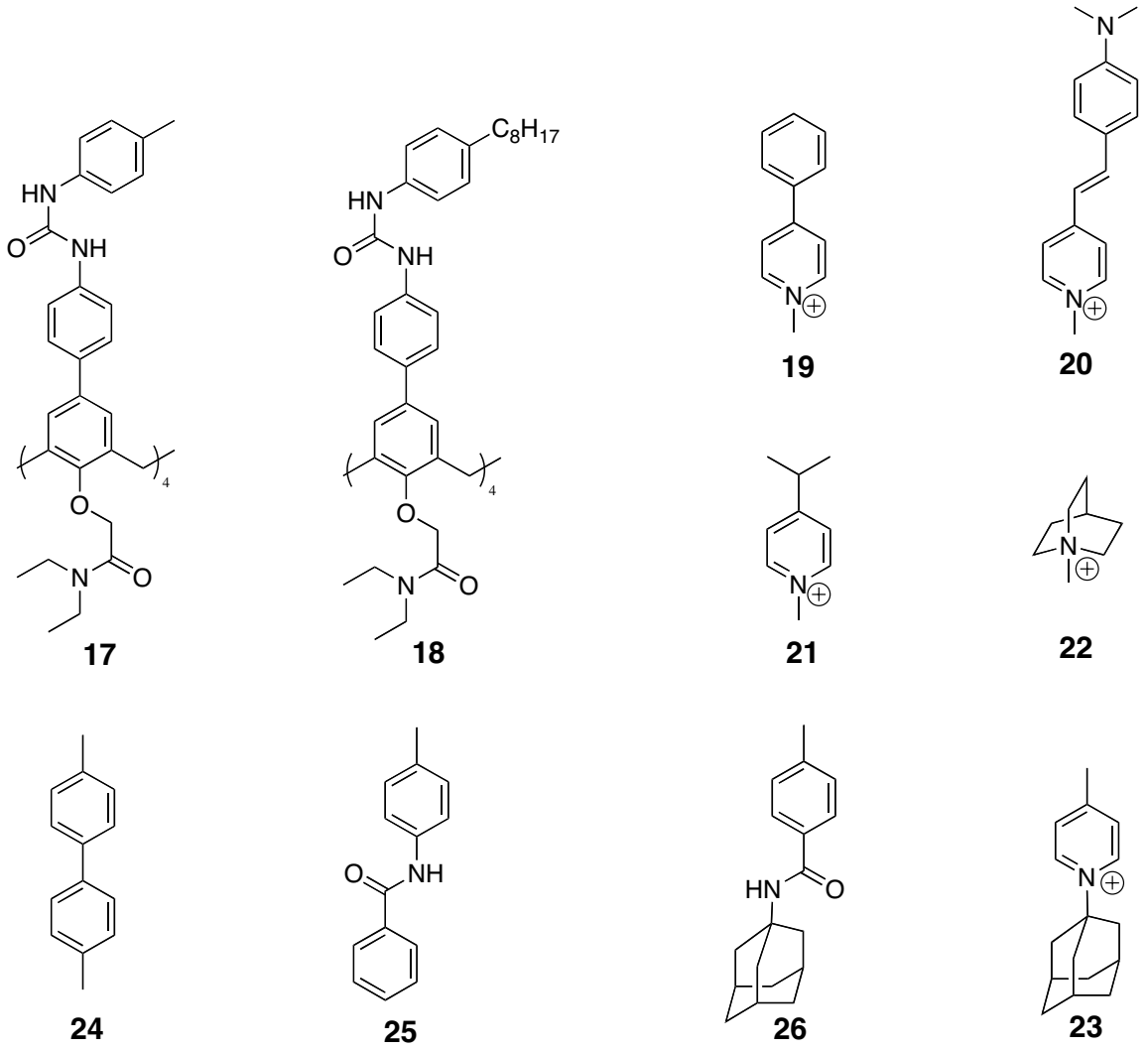


Figure 1-16. Extended Ureacalix[4]arene Derivatives and Guest Molecules

Dr. Bohmer's research group synthesized several different calix[4]arene derivatives with substituted ureas on the upper rim and pentyl, benzyl, or ethyl ester groups on the lower rim (Figure 1-17).[25] All of the derivatives **(27-29)** were found to form homodimers in apolar solvents and existed as monomers in polar solvents. Mixtures composed of two of the derivatives were made in all the possible combinations and studied by ^{1}H NMR. When the two derivatives were mixed together in dmso-d_6, the ^{1}H NMR spectrum was composed of the spectra of each derivative alone. When the two

derivatives were mixed together in apolar solvents, the spectrum contained three sets of signals. Two of the signals were from the two homodimers and one of the signals was from the heterodimer. The two homodimers and the heterodimer were found to exist in equal amounts without any preference for hetero or homodimerization.

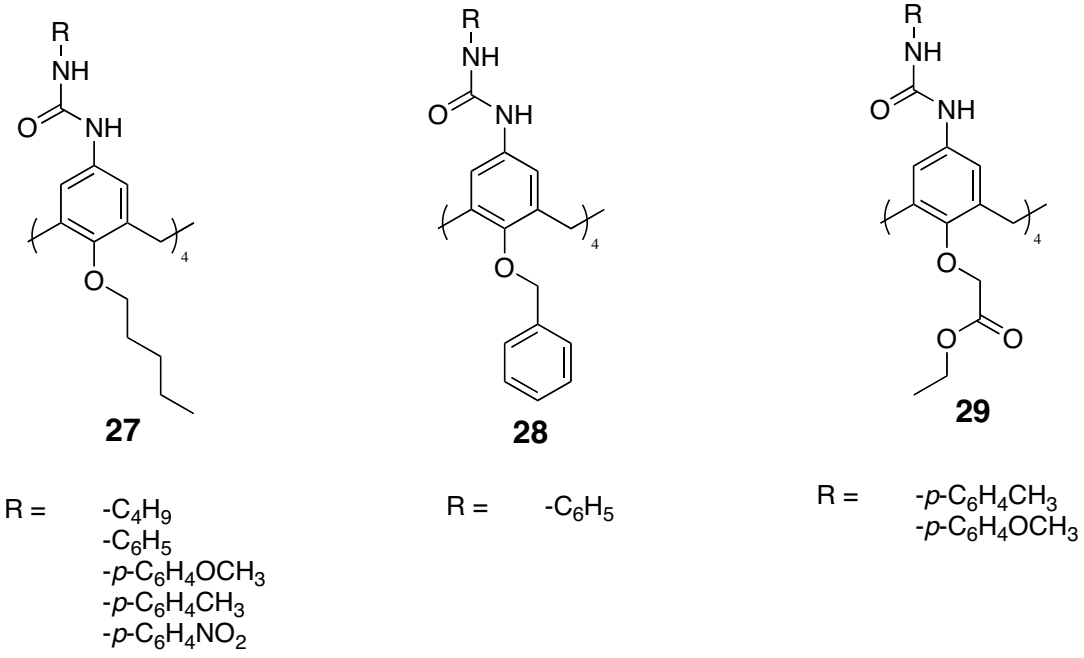


Figure 1-17. UreaCalix[4]arene Derivatives

Calix[4]arene derivative **30**, with propyl groups on the lower rim and tolyl ureas on the upper rim, was used to study the effects of the size and shape on the encapsulation of cationic guests (Figure 1-18).[26] Several guests were studied including bicyclic aliphatic molecules (**34-35**), flexible aliphatic molecules (**31, 33, 37**), and aromatic molecules (**32, 36, 38**). Complexes of capsule **30:30** with guests **33**, **35**, and **36** in the gas phase were studied by MS. The base peak corresponding to the capsule and one guest was seen for all of the complexes. When 10% methanol was added to the complex, the mass peak for

the complex went away and a peak for the monomer was seen. Competition studies were performed with all of the guests and studied by ESI. Figure 1-18 shows results of the competition experiment with **33** being the best guest. Guests **31** and **32** were too big to be encapsulated. This study further supports that size and shape are the most important factors in guest encapsulation. The guest that fits the cavity the best binds the tightest.

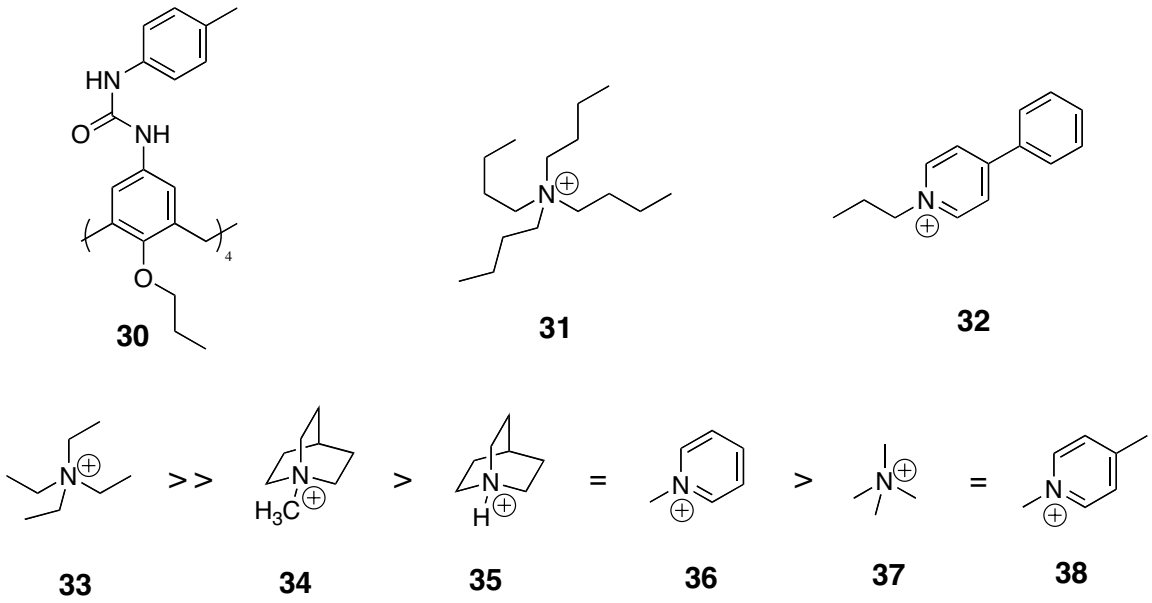


Figure 1-18. Tolylureacalix[4]arene and its Guest Molecules

A calix[4]arene derivative with tolylurea groups on the upper rim and decyl groups on the lower rim **(40)** was synthesized and studied for its ability to self-assemble into a homodimer.[27] Encapsulation studies were performed with the homodimer and various guests in cyclohexane-d_{12}. Guest escape from the complex was monitored by ^{1}H NMR over time at room temperature. Rate constants and half-life's for the various guests are listed in Table 1-4. Complexes with iodobenzene, *p*-xylene, trifluorotoluene, 1,4-bis(trifluoromethyl)benzene, 1,4-dioxane and cyclohexanone were not soluble in

cyclohexane-d_{12}. Toluene was seen to escape from the complex at a much faster rate than benzene, but cyclohexane and methylcyclohexane have very similar half-life's that are 2 orders of magnitude higher then benzene's. Benzene and bromobenzene form complexes of similar strength but changing from bromobenzene to chlorobenzene to fluorobenzene to 1,4-difluorobenzene increases the half-life's from 23 h to 40 h to 74 h to 1470 h, respectively. These studies show that by encapsulating an appropriate guest, the stability of the dimer can be increased by several orders of magnitude.

Table 1-4. Rate Constants for the Guest Escape (Exchange against C_6D_{12}) and Half-Life Times of the Complexes of **40:**guest**:40**

guest	k, h^{-1}	$\tau_{1/2}$, h
cyclohexane	3.68×10^{-4}	1880
methylcyclohexane	3.89×10^{-4}	1780
benzene	3.44×10^{-2}	20
fluorobenzene	9.38×10^{-3}	74
1,4-difluorobenzene	4.71×10^{-4}	1470
chlorobenzene	1.74×10^{-2}	40
bromobenzene	3.04×10^{-2}	23
iodobenzene	[a]	
toluene	1.64×10^{-1}	4.2
p-xylene	[a]	
α,α,α-trifluorortoluene	[a, b]	
1,4-bis-(trifluoromethyl)benzene	[b]	
chloroform	2.36×10^{-1}	2.9
tetrachloromethane	3.17×10^{-4}	1120
1,4-dioxane	[a]	
cyclohexanone	[a]	

[a]Complex not soluble in cyclohexane. [b]Capsule is not soluble in an excess of the guest.

1.3.2 Hydrogen Bonded Chiral Capsules

Chiral capsules were synthesized from calix[4]arene derivatives with phenyl ureas substituted with aryl **(39-40)**, sulfonylaryl **(41)**, or chiral **(42-52)** groups on the upper rim (Figure 1-19).[28] These capsules were studied by ^{1}H NMR for asymmetric binding of

several guests, such as (1*R*)-(+)-nopinone **(53)**, (1*R*)-(-)-myrtenal **(54)**, (1*R*)-(+)-camphor **(55)**, and tricyclene **(56)** in *p*-xylene-d_{10}. Encapsulation of these guests in **39:39** reduces the symmetry of the capsule in the ^{1}H NMR because the top and bottom halves are no longer magnetically equivalent. Compound **53** caused a doubling of the capsule resonances when encapsulated. When symmetrical guest **56** is encapsulated, two different sets of peaks for the guest are seen. These different sets of peaks correspond to capsules with guests in different orientations. Unequal ratios in the peaks shows that there is a preferred orientation and that the guest is not free to rotate inside the capsule. When **39** and **41** were mixed together, the heterodimer **39:41** was formed exclusively. The heterodimer was found to be more stable than the homodimers **39:39** and **41:41** for two reasons.[29] The first reason is that the increased acidity of the sulfonylurea urea proton complements the increased basicity of the aryl urea proton. The second reason is that NOESY studies found that the aryl groups of both ureas are close together. The aryl-aryl interactions help stabilize the heterodimer. When **41** was mixed with an alkylurea derivative, only 10% heterodimerization was seen by ^{1}H NMR. Encapsulation of **54** within heterodimer **39:41** gave two sets of resonances for the guest molecule. The encapsulated guest must have two preferred orientations within the capsule. When **53** was encapsulated in heterodimer **39:42** in *p*-xylene-d_{10}, only one set of peaks was observed indicating that the guest has one preferred orientation. Encapsulation of **53** in capsule **39:45** provided the diastereomer of **39:53:42** and gave a different set resonances for both the capsule and the guest. Complex **39**:(+)-nopinone:**42** is equivalent to complex **39**:(-)-nopinone:**45** by ^{1}H NMR. Complexes of capsule **39:42** with each enantiomer of nopinone gave signals that resembled the above diastereomeric complexes. This proved that

capsules **39:42** and **39:45** are diastereomers of each other. Each capsule contained hydrogen bonds rotating the opposite way.

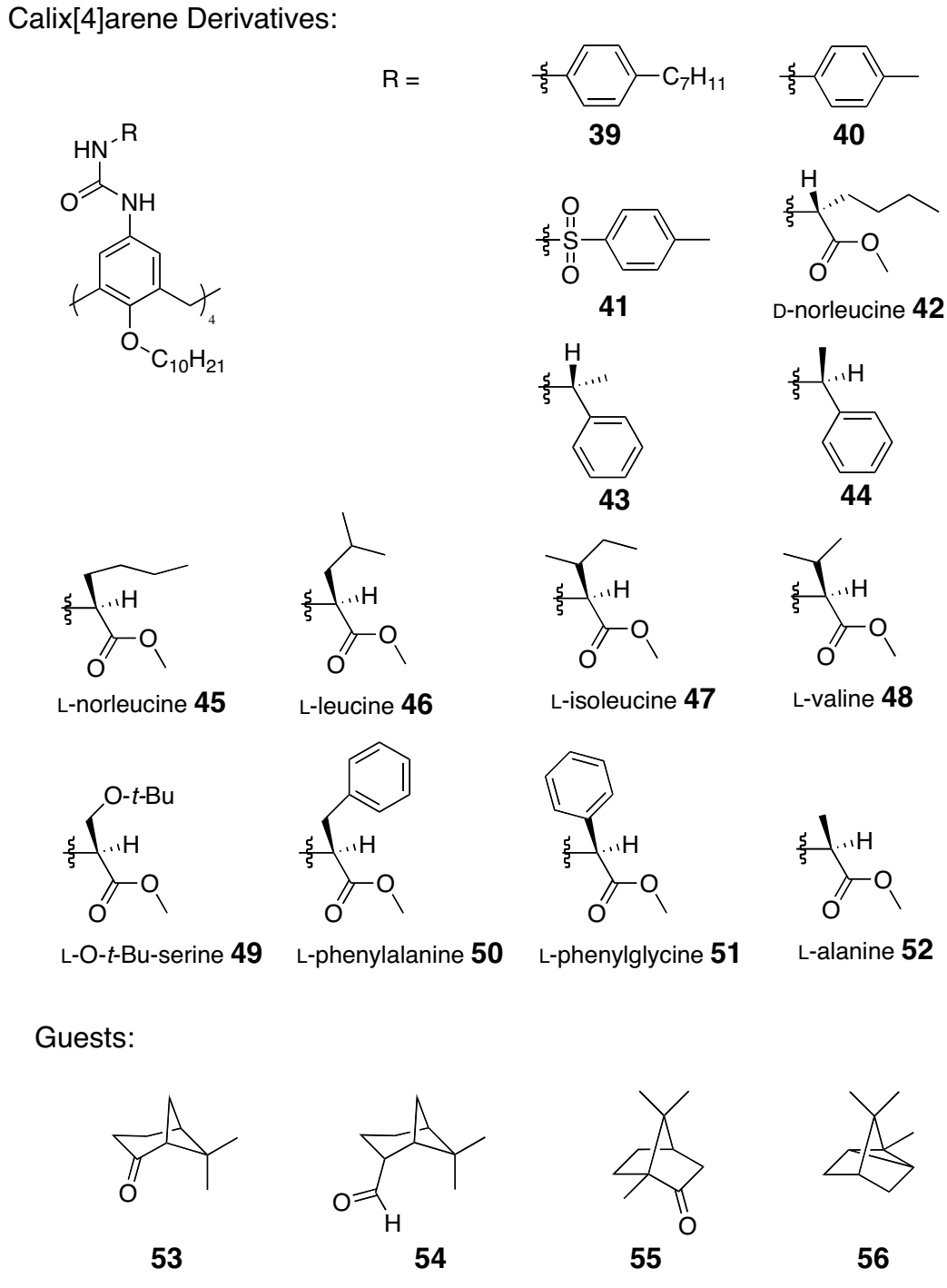


Figure 1-19. Chiral Ureacalix[4]arene Derivatives and Guest Molecules

Calix[4]arene derivatives substituted with amino acid ureas (**45-52**) on the upper rim (Figure 1-19) were synthesized and studied for their ability to form homodimers and heterodimers with **40** or **41**.[30] These heterodimers were also studied for their ability to encapsulate (*R*)-(+)-3-methylcyclopentanone and (*S*)-(+)-methylcyclopentanone. The isoleucine **(47)** and valine **(48)** derivatives were the only derivatives found to form homodimers. All of the derivatives formed heterodimers with the tolylurea derivative **(40)** in both chloroform-*d* and benzene-d_6 (Table 1-5) but did not form heterodimers with the tolylsulfonylurea derivative **(41)**. Changing the solvent from chloroform-*d* to benzene-d_6 increased the stability of the heterodimers formed. The valine and isoleucine urea derivatives heterodimerize exclusively with **40** in benzene-d_6. NOE experiments showed that the β-branched amino acids have favorable contacts with the tolyl urea of the calix[4]arene stabilizing the heterodimers over the homodimers. Most of the capsules formed in only one of the two diastereomeric forms with the hydrogen bonds going either clockwise or counterclockwise. Circular dichroism spectroscopy proved the one handedness of the capsules. Molecular modeling of capsule **40:48** suggested that the CD spectrum represents the coupling between the dipoles of the tolyl group of **40** and the calix[4]arene rings of **48**. This alignment of tolyl and calix[4]arene groups is only possible when the ureas are rotated in the clockwise direction. Because the dimers have hydrogen bonds going in one direction, encapsulation of enantiomers gives rise to two different signals. When a racemic guest is encapsulated within heterodimer **40:41**, which is racemic with respect to its hydrogen bond orientation, four signals are seen, which correspond to the two enantiomeric guests and the two different directions in hydrogen bonds. When (*R*)-(+)-3-methylcyclopentanone is encapsulated in heterodimer **40:41**, two

signals are seen, one for each hydrogen bond direction. When (*R*)-(+)-3-methylcyclopentanone is encapsulated in capsule **40:47**, only one signal is seen because of the one handedness of the capsule.

Table 1-5. Percentage of Heterodimer Formed upon Combination of Arylurea **40** and Amino Acid Derivatives **45-52**[a]

Amino Acid Derivative	$CDCl_3$	C_6D_6
norleucine	50%[b]	90%
leucine	50%[b]	90%
isoleucine	90%[b]	100%
valine	>90%[b]	100%
serine	25%	75%[b]
phenylalanine	<10%	73%
phenylglycine	43%[c]	90%[d]
alanine	<10%[e]	50%[f]

[a]Unless otherwise specified the percentages shown reflect formation of one of two possible heterodimers. Percentages vary ±5%. [b]<5% non-specific aggregation. [c]6.4:1 ratio of heterodimers. [d]1.9:1 ratio of heterodimers. [e]Broad spectrum. [f]3.4:1 ratio of heterodimers.

Dr. De Mendoza's research group synthesized calix[4]arene derivatives with either four Leu-octylamides or four ^{L}Leu-^{D}Leu-OMe dipeptides on the upper rim (Figure 1-20).[31] Two possible dimer structures were surmised (Figure 1-20). The first dimer structure **59** is formed when the ureas hydrogen bond to each other and the side chains stick out away from the interface. The second structure **60** consists of the ureas hydrogen bonding to the peptide amides forming a larger extended cavity. Calix[4]arene **57** did not dimerize under any of the experimental conditions. The dipeptide derivative **58** dimerized in methylene chloride-d_2 and toluene-d_8 with association constants of 20 M^{-1} and 5100 M^{-1}, respectively. The capsule structure was determined be structure **59** with the ureas hydrogen bonding and the side chains sticking out. The side chains were found to form

additional hydrogen bonds between the amide donors of one chain and the carbonyl of an adjacent chain. These additional hydrogen bonds further stabilize the dimer.

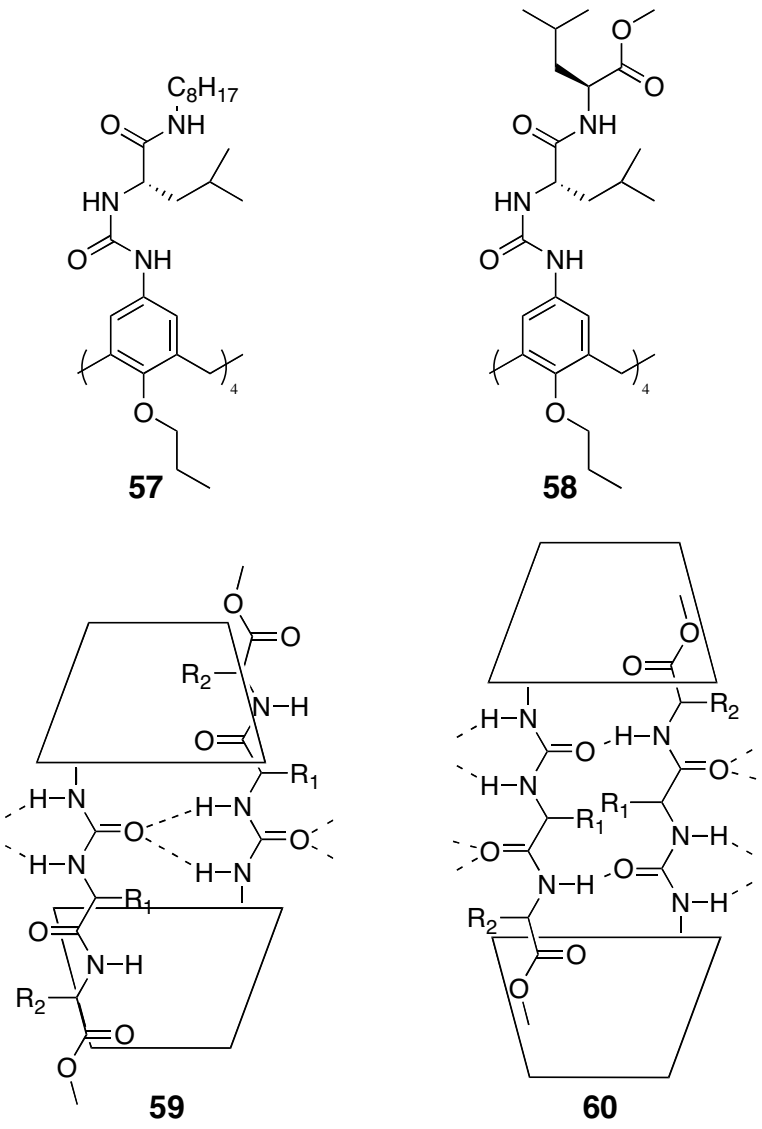


Figure 1-20. Chiral UreaCalix[4]arene Derivatives and Proposed Dimer Structures

1.3.3 Hydrogen Bonded Capsules with Higher Kinetic Stabilities

Hydrogen bonded capsules with higher kinetic stabilities have been synthesized from calix[4]arene derivatives with ureas on the upper rim substituted with large bulky groups (Figure 1-21).[32] Homo and heterodimers of the derivatives were studied by ^{1}H NMR in benzene-d_6 (Table 1-6).

Table 1-6. Dimerization of Tetra-Ureas **61-65**[a]

Compound	**61**	**62**	**63**	**64**	**65**
61	+	0[b]	50[c]	39[c]	78[b]
62	0[b]	0[b]	0[b]	0[b]	0
63	50[c]	0[b]	+	31[c]	0[b]
64	39[c]	0[b]	31[c]	+	95[b]
65	78[b]	0	0[b]	95[b]	-

[a]For each pair the formation of dimers is indicated by +. Additionally, the amount of heterodimers present in a 1:1 mixture in benzene-d_6 at a total concentration of c = 2.5 mM is reported in %. [b]Plus one homodimer and one unpaired monomer. [c]Plus two homodimers.

Benzene was used because it is a good solvent and guest for the dimers. **64** and **65** were found to form a heterodimer almost exclusively. The heterodimer **64:65** was favored over a mixture containing one homodimer **64:64** and one monomer **65**. The half-life of the complex **61:65** with encapsulated benzene was determined to be ~130 minutes and ~60 hours for **64:65** with encapsulated benzene. When **64** and **65** were dissolved in toluene or *p*-xylene, no heterodimer was formed only homodimer **64:64** and monomer **65**. Benzene seems to be a more favorable guest than either toluene or *p*-xylene and is able to promote the formation of the more strained heterodimer **64:65** whereas the toluene and *p*-xylene are not. Heterodimer **64:65** with encapsulated benzene was stable at 40 °C for 18 hours in cyclohexane-d_{12} showing the increased kinetic stability. Molecular modeling of homodimer **65:65** showed that the inner cavity is not big enough to hold a benzene

molecule.[33] This inability to encapsulate benzene is the reason that **65** does not homodimerize in benzene. To see if a smaller guest would induce homodimerization, **65** was refluxed in methylene chloride in the presence of tetramethylammonium iodide and chloride. Both complexes were isolated and characterized by ^{1}H NMR in chloroform-*d*. When complex **65**:Me_4N^+:**65** was dissolved in DMSO-d_6, the complex degraded slowly into its monomer and guest with a half-life of ~93 hours. The authors rationalize that mechanical entanglement of the bulky side chains protects the urea hydrogen bonds from the DMSO molecules slowing down the dissociation.

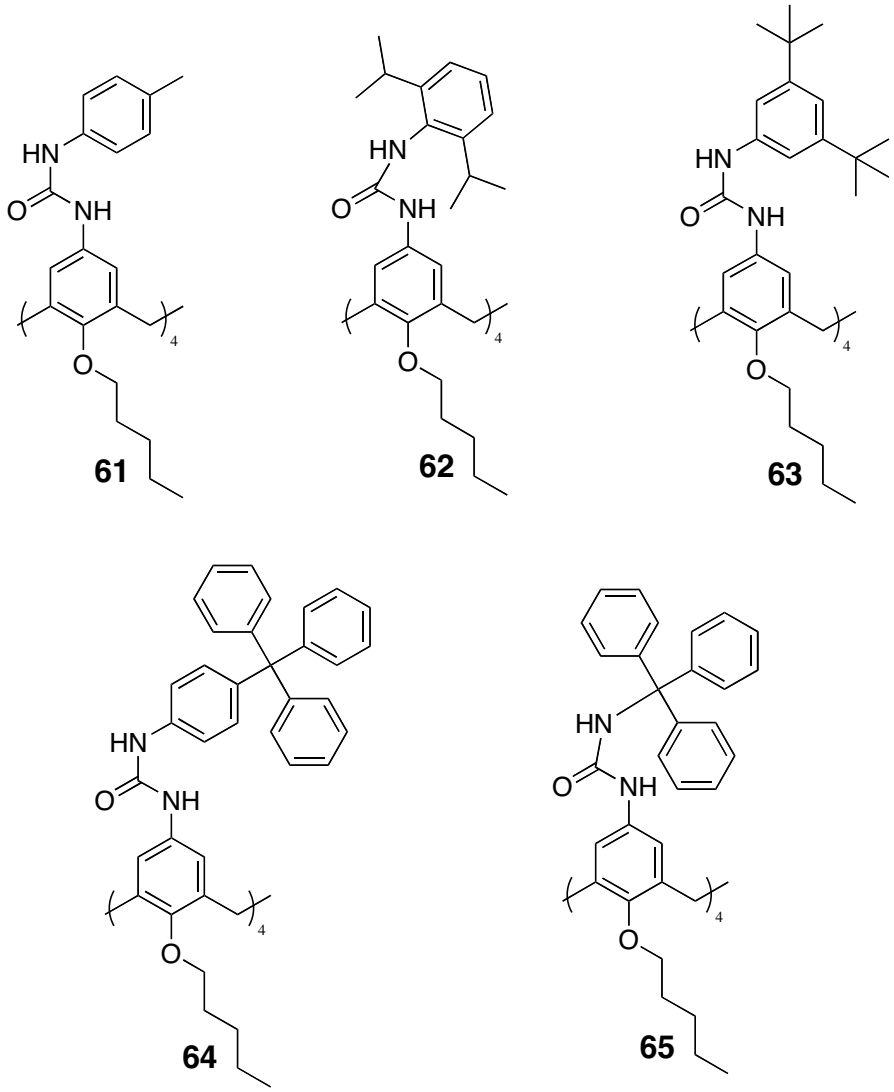


Figure 1-21. Ureacalix[4]arene Derivatives with Bulky Substituents

Rigid calix[4]arene derivatives with two diethyleneglycol tethers on the lower rim attached to adjacent phenol oxygens were synthesized.[34] These derivatives were substituted on the upper rim with tolyl, *t*-butyltrityl, or sulfonyltolyl ureas (Figure 1-22). The rigid derivatives, **66a** and **66b**, were compared to their flexible counter parts **67a** and **67b**. Both of the rigid derivatives formed homodimers in chloroform-*d*. Disproportionation experiments were performed between the rigid derivatives and flexible derivative **67c** in chloroform-*d*. Calix[4]arene **67a** was previously seen to form a heterodimer exclusively when mixed with **67c**. No heterodimers were seen in any of the mixtures of **67c** with the rigid derivatives even after eight equivalents of **67c** was added. Homodimers of the rigid derivatives were tested to see how much DMSO could be tolerated before the dimer dissociated into a 1:1 ratio of dimer to monomer. Homodimer **66a:66a** required 8% DMSO by volume and **66b:66b** required >18% DMSO. This is more than four times the amount of DMSO tolerated by the flexible derivatives. Homodimer **66b:66b** was found to be ~500 times more stable than **66a:66a** in chloroform with 12% DMSO. Complexes of the rigid homodimers **66a:66a** and **66b:66b** and the flexible homodimer **67b:67b** with encapsulated benzene were dissolved in benzene-d_6 and monitored for the release of the encapsulated benzene. The half-life's were determined to be 82 s, 2460 s, and 550 s, respectively. Half-life times for the release of cyclohexane in a similar experiment were found to be 245 hours for **66a:66a** and 6.3 hours for **67a:67a**. Overall the rigid derivatives were found to have increased stability compared to their flexible counterparts with the bulky side chain derivatives being more stable then the tolyl side chain derivatives.

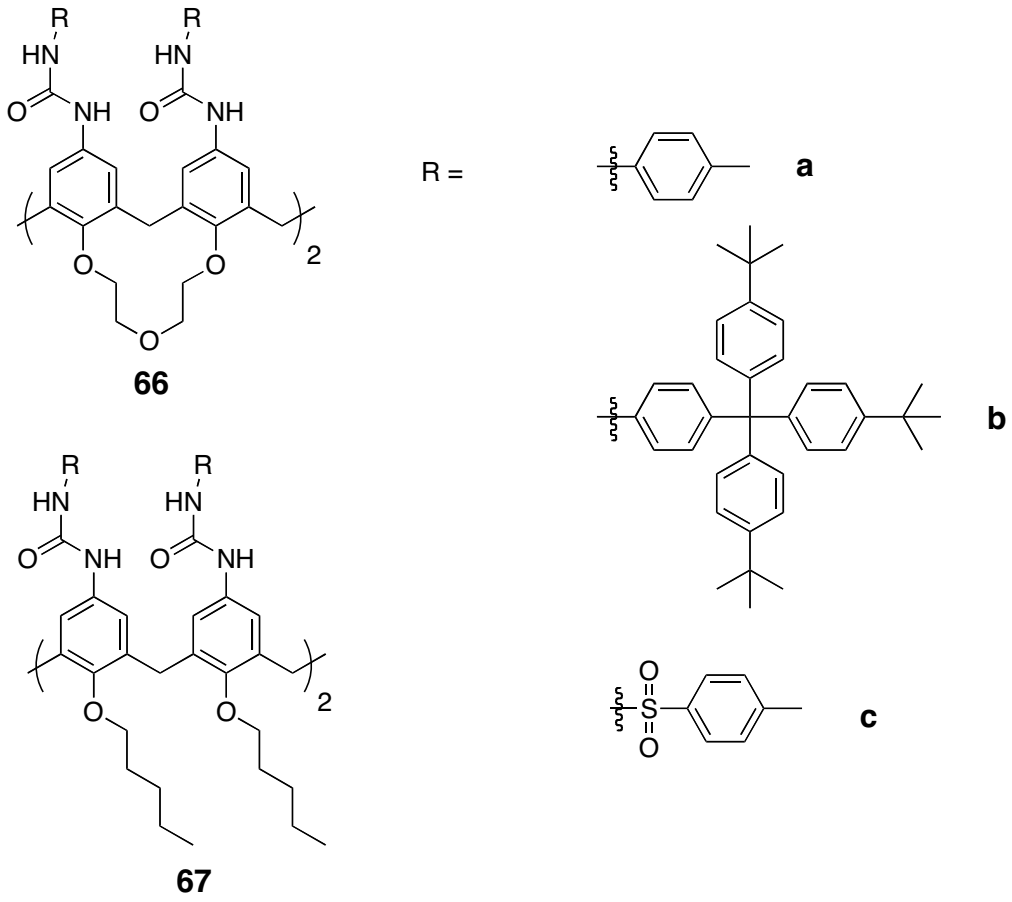


Figure 1-22. Rigid and Flexible Ureacalix[4]arene Derivatives with Bulky Substituents

Dr. Shuker's group synthesized calix[4]arene derivative **68** which was propylated on the lower rim and substituted on the upper rim with four *C*-linked alanines (Figure 1-23).[35] Alaninocalix[4]arene **(68)** was found to self-assemble into homodimers in a solution of methanol-d_4 with 4% D_2O. The association constant for the derivative in the methanol-d_6/4% D_2O solution was calculated to be 29,000 M^{-1}. Two possible models were theorized for the dimerization (Figure 1-23). In the first model **(69)**, the dimer is held together by eight hydrogen bonds. In the second model **(70)**, the dimer is held together by sixteen hydrogen bonds making it more favorable than the first model. The dimer **68:68** was studied by ^1H NMR for its ability to bind various amino acids. Two

amino acids, arginine and lysine, caused dramatic shifts in the ^{1}H NMR upon addition. Mass spectroscopy of the arginine or lysine and homodimer mixture gave a peak that corresponded to a 1:1 complex of **68** and either arginine or lysine. The amino acid caused the dimer to disassociate so that it could bind in the cavity of the calix[4]arene monomer.

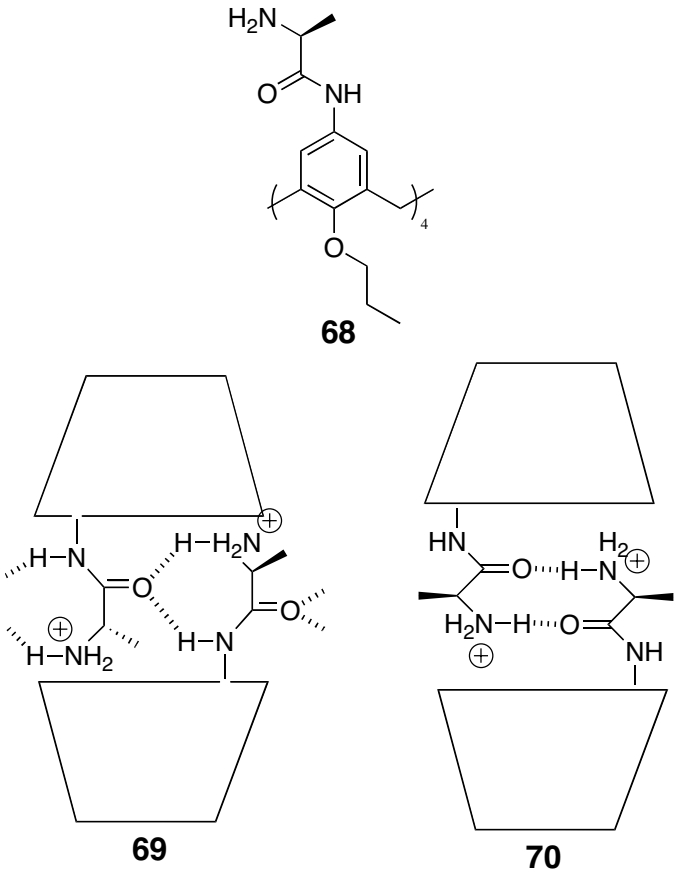


Figure 1-23. *C*-Linked Alaninocalix[4]arene and its Possible Dimer Structures

1.3.4 Ionic Bonded Capsules in Polar Solvents

Dr. Reinhoudt's group synthesized several calix[4]arene derivatives that were substituted with substituted amidinium **(71-74)** and sulfonato **(75)** groups on the upper rims (Figure 1-24).[36]

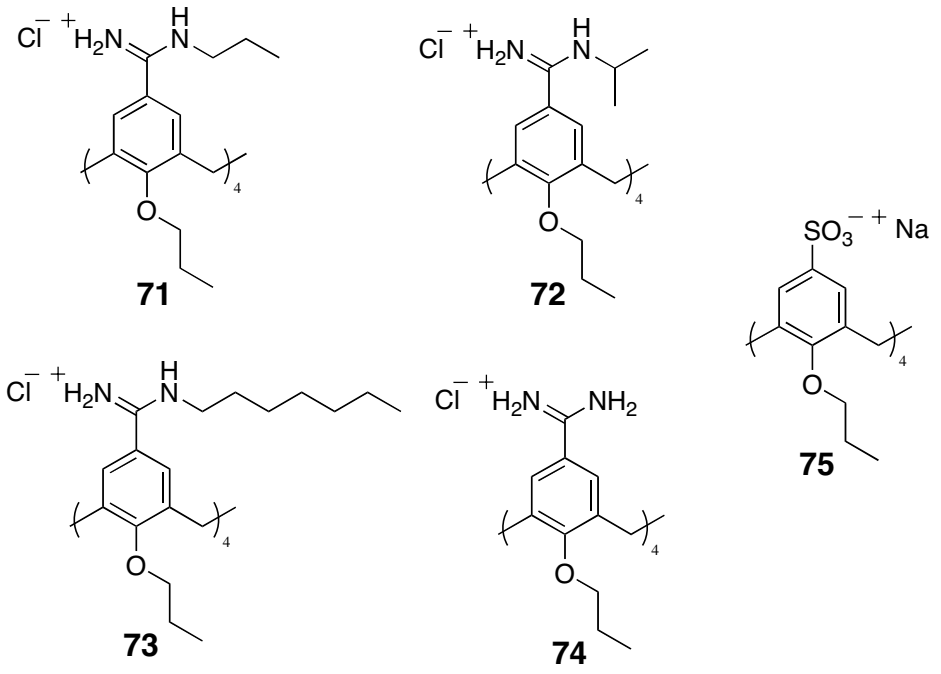


Figure 1-24. Ionic Calix[4]arene Derivatives

The amidinium derivatives were found to dimerize with the sulfonato derivative through ionic interactions in methanol/water solutions with up to 40% water. The proton signals for the amidinium propyl side chain of **71** were shifted upfield in the ^{1}H NMR spectrum of **71:75**. This upfield shift must be caused by the encapsulation of one of the side chains inside the cavity upon dimerization. The protons on the isopropyl side chain of derivative **72** were shifted upfield in the ^{1}H NMR spectrum of **72:75**. Similar to the propyl derivative, one of the isopropyl side chains must fit inside the cavity upon dimerization causing the upfield shift. The protons of the heptyl side chain of derivative **73** were not shifted upfield in the ^{1}H NMR spectrum of **73:75**. The heptyl side chain must be too large to fit inside the cavity upon dimerization. Association constants, enthalpy, and entropy were calculated by isothermal calorimetry titration (Table 1-7).

Table 1-7. Thermodynamic Parameters for the Formation of Assemblies **71-74** with **75** as Determined by ITC[a]

assembly	K_a (M^{-1})	ΔH (kJ mol^{-1})	ΔS (J K^{-1} mol^{-1})
71:75	(8.5 ± 1.4) x 10^6	14.1 ± 0.1	180 ± 2
71:75[b]	(2.1 ± 0.5) x 10^5	11.6 ± 0.5	141 ± 3
72:75	(6.4 ± 1.7) x 10^6	13.7 ± 0.2	176 ± 2
73:75	(1.1 ± 0.1) x 10^6	17.9 ± 0.1	176 ± 1
74:75	(1.9 ± 0.3) x 10^6	33.3 ± 0.3	231 ± 2

[a]Measured in MeOH/H_2O (χ_{water} = 0.4) at 298 K, background electrolyte: 1 x 10^{-2} M Bu_4NClO_4. [b]Background electrolyte: 1 x 10^{-2} M TMACl.

The positive enthalpy values result from the enthalpy needed to desolvate the charged amidinium groups minus the enthalpy needed for the assembly. The positive entropy values are caused by the release of highly ordered solvent molecules into the bulk media during assembly. Dimer **71:75** was studied for its ability to bind tetramethylammonium chloride, tetramethylammonium bromide, or tetrabutylammonium chloride in methanol-d_4. Addition of excess of tetramethylammonium bromide or chloride causes a downfield shift in the protons of the propyl side chains. This is caused by the encapsulation of the guest and the ejection of the propyl side chain from the cavity back into bulk solution. When an excess of tetrabutylammonium chloride was added, no change was seen in the ^{1}H NMR because the guest was too large to fit inside the cavity. No change in chemical shift was observed for the guest protons when encapsulated because an excess of the guest was used, causing the ^{1}H NMR signal to be the average of the free and encapsulated guest signals. When one equivalent of tetramethylammonium chloride was added to a solution of the dimer, a small shift was seen in the guest protons by ^{1}H NMR. Fitting the data to a 1:1 binding model gave an association constant of 170 M^{-1} for the guest encapsulation in methanol-d_4. Acethylcholine, a neurotransmitter, and *N*-

methylquinuclidinium were also studied for encapsulation. Addition of excess acethylcholine also caused a downfield shift in the protons from the propyl side chain. When one equivalent of acethylcholine or *N*-methylquinuclidinium was added, an upfield shift for the guest protons was observed. Using a 1:1 binding model, an association constant of 37 M^{-1} and 24 M^{-1} was calculated for the binding of acethylcholine and *N*-methylquinuclidinium respectively.

Ionic calix[4]arene derivatives with butyl groups on the lower rim and either four amines, aminomethyls, carboxyls, phosphonates, phosphonatomethyls, or pyrazolyls on the upper rim were synthesized (Figure 1-25) and studied by ^{1}H NMR dilution studies and Job plots for their ability to form heterodimers in methanol.[37, 38] Association constants calculated for these heterodimers ranged from 2 x 10^3 and 7 x 10^5 M^{-1} (Table 1-8).

Table 1-8. Binding Constants, K_a (M^{-1}), and Gibbs Free Energies of Association (kcal mol^{-1}) in Methanol at 25 °C from NMR Titrations between All Possible Combinations of Calix[4]arene Half-Spheres[a]

complex[b]	benzylphosphonate **76**	ΔG^c	carboxylate **79**	ΔG^c	phosphonate **80**	ΔG^c
pyrazolium **78**[d]	(4±0.1)x10^3	-4.8	no shifts	-	(2±0.6)x10^3	-4.4
ammonium **77**	(4±0.4)x10^5	-7.5	(3±1.1)x10^4	-6.0	(7±2.5)x10^5	-7.8
anilinium **81**	(7±1.0)x10^3	-5.2	(7±1.3)x10^3[d,e]	-5.2	(1±0.5)x10^4[f]	-5.4

[a]Unless stated otherwise. [b]Errors are standard deviations from the nonlinear regressions. [c]In kcal mol^{-1}. [d]Determined by dilution titration. [e]In DMSO-d_6. [f]In D_2O/CD_3OD (1:4).

The authors found that the strongest dimers were formed from the monomers with the largest difference in pK_a's between the acidic and basic groups on the upper rims. The aminomethyl derivative **77** (pK_a ≅ 9) formed the strongest dimers with the two phosphonate derivatives **(76** and **80)** (pK_a ≅ 2). The least basic pyrazole derivative **78**

($pK_a \cong 2.5$) did not dimerize with the less acidic carboxy derivative **79** ($pK_a \cong 5$) and formed weak hydrogen bonded dimers with the phosphonate derivatives. Encapsulation of tetramethylammonium, phenylalanine, *N*-methylpyrazinium iodide and *N*-methylated nicotinamide by the capsules was also studied by ^{1}H NMR[38]. No guest encapsulation was seen. When *N*-methylpyrazinium iodide or *N*-methylated nicotinamide was added to a solution of the phosphonate derivative **80**, a 1:1 complex was formed between the calix[4]arene and the guest. The cationic anilinium derivative **81** was added to the preformed phosphonate:guest complex but no capsule:guest complex was seen by ^{1}H NMR. Instead, the guest was released upon capsule formation.

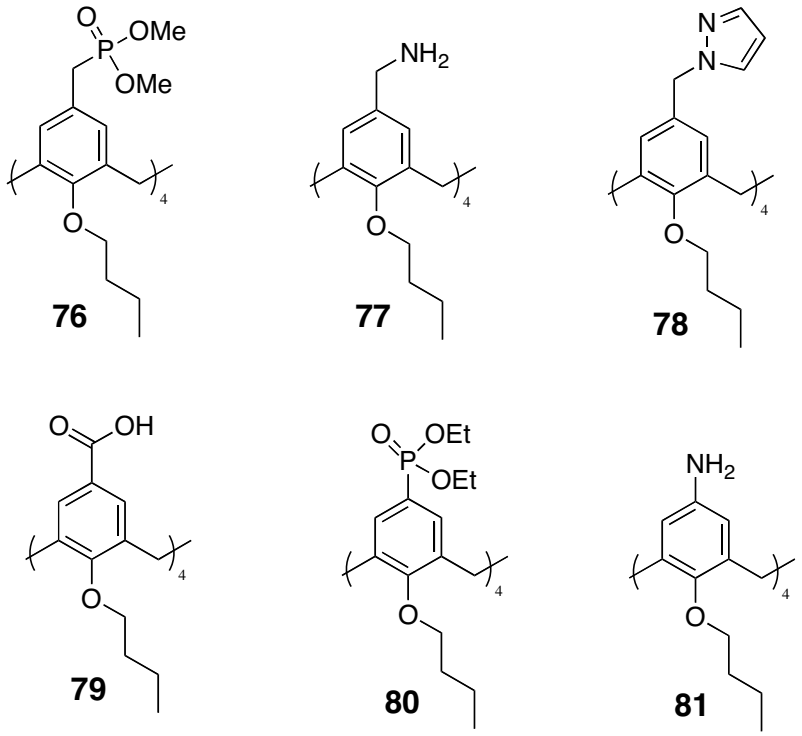


Figure 1-25. Calix[4]arene Derivatives that Dimerize through Ionic Interactions

A water-soluble capsule has been synthesized and studied for its ability to encapsulate guests in polar solvents.[39] The heterodimer **82:83** is formed from two calix[4]arene derivatives (Figure 1-26). The first derivative **82** is substituted on its upper rim with an alanine linked through its *N*-terminus. The second derivative **83** is substituted on its upper rim with a propylamidine moiety. Both derivatives have ethoxyethyl groups on their lower rims. The monomers and capsule are completely soluble in H_2O at pH 9. Capsule formation can be monitored by the upfield shift of the propylamidine groups by ^{1}H NMR. The upfield shift is caused by the encapsulation of one of the propyl groups from the amidines upon dimerization. The association constant was calculated to be 3.3 x 10^4 M^{-1} by isothermal calorimetry measurements. Encapsulation was studied using *N*-methylquinuclidinium cation as a guest. Addition of 30 equivalents of the guest to the capsule resulted in a downfield shift in the propylamidine groups caused by the ejection of the propyl group from the cavity of the capsule upon guest encapsulation.

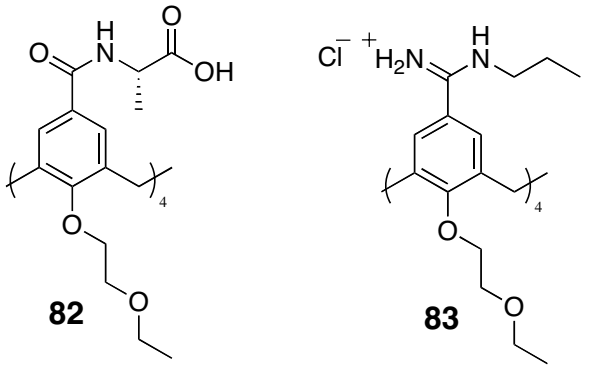


Figure 1-26. Water-Soluble Ionic Calix[4]arene Derivatives

1.4 Conclusion

Molecular capsules can be formed from many different molecules. Two of these molecules are cavitands and calix[4]arenes. Cavitands form capsules through the covalent bonding of two cavitands rim to rim. These capsules are called carcerands and hemicarcerands. Carcerands encapsulate guest molecules irreversibly upon formation. Hemicarcerands encapsulate guest molecules reversibly. Guests can enter and exit the capsule at elevated temperatures but cannot enter or exit the capsule at room temperature. Calix[4]arene derivatives form noncovalent capsules that are held together with hydrogen or ionic bonding. These capsules encapsulate guests reversibly in both nonpolar and polar solvents. In order to be used in biological applications, the capsules must be water-soluble. There are only a few examples of water-soluble capsules in literature to date.

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CHAPTER 2

CALIX[4]ARENE DIMERS

2.1 Calix[4]arene Dimers

Molecular recognition is a fast and growing field. It is the synthesis and study of molecules capable of recognizing and binding one another through intermolecular interactions such as hydrogen bonds, π-stacking, hydrophobic interactions, electrostatic interactions, and van der Waals interactions. These molecules can then be used as receptors, transport agents, catalysts, biocatalysts, supramolecular arrays, and for drug transport and delivery. Molecular recognition can be used to create self-assembling capsules.[1] A self-assembling capsule is a supramolecular structure made up of two or more molecules that come together through noncovalent, reversible interactions to form an enclosed cavity. If an appropriate guest molecule is mixed in with the monomers, the guest will be encapsulated within the cavity.

To utilize the capsules for a broader range of applications, the capsules and capsule-guest complexes must self-assemble and be soluble in polar, protic solvents and nonpolar solvents. There are many examples of self-assembling molecular capsules in literature that assemble through hydrogen bonding.[2-12] Hydrogen bonds are formed from electrostatic interactions between the dipole of a hydrogen donor (AH) and hydrogen acceptor (B). The small size of the hydrogen atom allows the donor and acceptor to come into close contact increasing the strength of the dipole-dipole interactions. Hydrogen bonds vary in strength from 1 to 10 kcal/mol depending on the atoms in the donor and acceptor groups.[13, 14] Most of these capsules assemble in nonpolar solvents and the

addition of even small amounts of polar solvents disrupts the self-assembly. This makes them unsuitable for many applications. There are only a few know examples of hydrogen bond mediated self-assembly in polar solvents.[15-18]

Ionic bonds are bonds formed through the electron transfer from a negatively charged ion to a positively charged ion. The energy cost of the electron transfer is overcome by the energy gained from the favorable electrostatic attraction between the ions. The ionic bond formed between a carboxylate ion and an alkylammonium ion has a Gibbs free energy of ~5 kJ/mol in water.[19, 20] An amide-amide hydrogen bond has a Gibbs free energy of ~5 kJ/mol in chloroform.[20] Nonpolar solvents are known to greatly increase the strength of noncovalent interactions such as ionic and hydrogen bonding. The fact that the ionic bond has a similar strength in water to that of the hydrogen bond in chlorform demonstrates the increased strength of ionic bonds over hydrogen bonds. Some recent publications report the synthesis of molecular capsules that assemble through ionic interactions in polar solvents.[21-25] These monomers dimerize more readily in polar solvents due to the increased bond strength of ionic bonds over hydrogen bonds. Calix[4]arenes derivatives substituted with charged functionalities on the upper rim and propyl groups on the lower rim were synthesized. These derivatives dimerize through ionic interactions in polar solvents forming both heterodimers and homodimers. These dimers will be used to encapsulate various guest molecules. Although the ionic propoxycalix[4]arene monomers are water-soluble, the heterodimers are not. This is due to the shielding of the charges upon assembly, leaving only the propyl groups on the lower rim exposed to the polar solvent. To use calix[4]arene capsules for drug delivery and other biological applications, the capsules must be water-soluble. Calix[4]arene

derivatives are being synthesized with hydroxy ethyl groups instead of the propyl groups on the lower rim. When the charged hydroxyethoxycalix[4]arene derivatives dimerize, the alcohols will be exposed to the polar solvent increasing the water-solubility of the capsules.

2.2 Calix[4]arene Heterodimers

Several calix[4]arene derivatives propylated on the lower rim and substituted on the upper rim with various functional groups have been synthesized. Examples include *C*-linked-alaninocalix[4]arene (**84**), *N*-linked-alaninocalix[4]arene (**85**), anilinocalix[4]arene (**86**), carboxycalix[4]arene (**87**), carboxyphenylcalix[4]arene (**88**), amidinocalix[4]arene (**89**), and aminomethylcalix[4]arene (**90**) (Figure 2-1). *C*-linked-alaninocalix[4]arene (**84**) was synthesized by Dr. Beth Brewster.[16] Carboxyphenylcalix[4]arene (**88**) was synthesized and studied by Dr. Kevin Caran. These derivatives heterodimerize in polar solvents. Figure 2-2 shows cartoons of the three different types of heterodimers studied: a dimer assembled from two monomers without spacers (**A**), a dimer assembled from one monomer without and one monomer with a spacer (**B**), and a dimer assembled from two monomers that both contain spacers (**C**).

All of the dimers were studied by ^{1}H NMR dilution studies in 95% dimethyl sulfoxide-d_6 (DMSO-d_6) or 95% methanol-d_4 (CD_3OD) with 5% phosphate buffer. Along with the dilution studies, the dimers were analyzed using Job Plots. A Job Plot is a graph that plots the change in chemical shift multiplied by the mol fraction *versus* the mol fraction. The ^{1}H NMR spectra from both the Job Plots and the dilution studies have sharp

peaks that are consistent with the formation of dimers and not larger assemblies, which would have broader peaks.

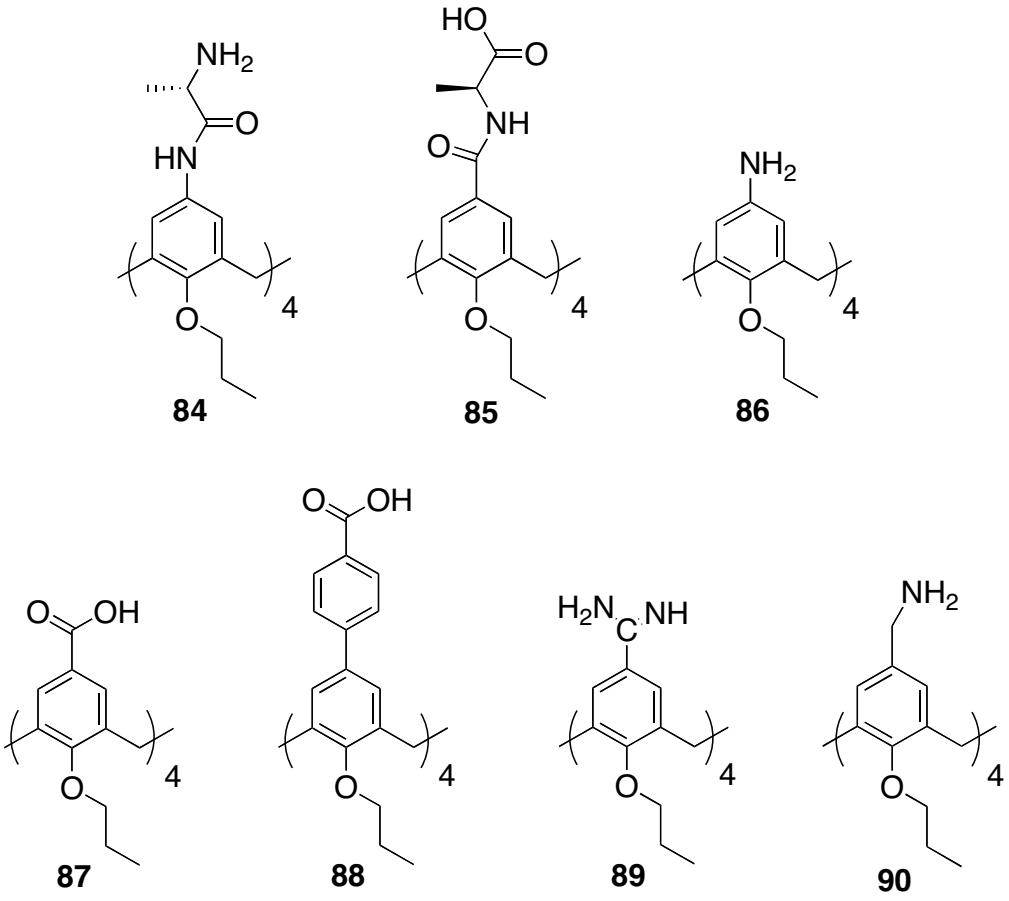


Figure 2-1. Calix[4]arene Heterodimer Derivatives

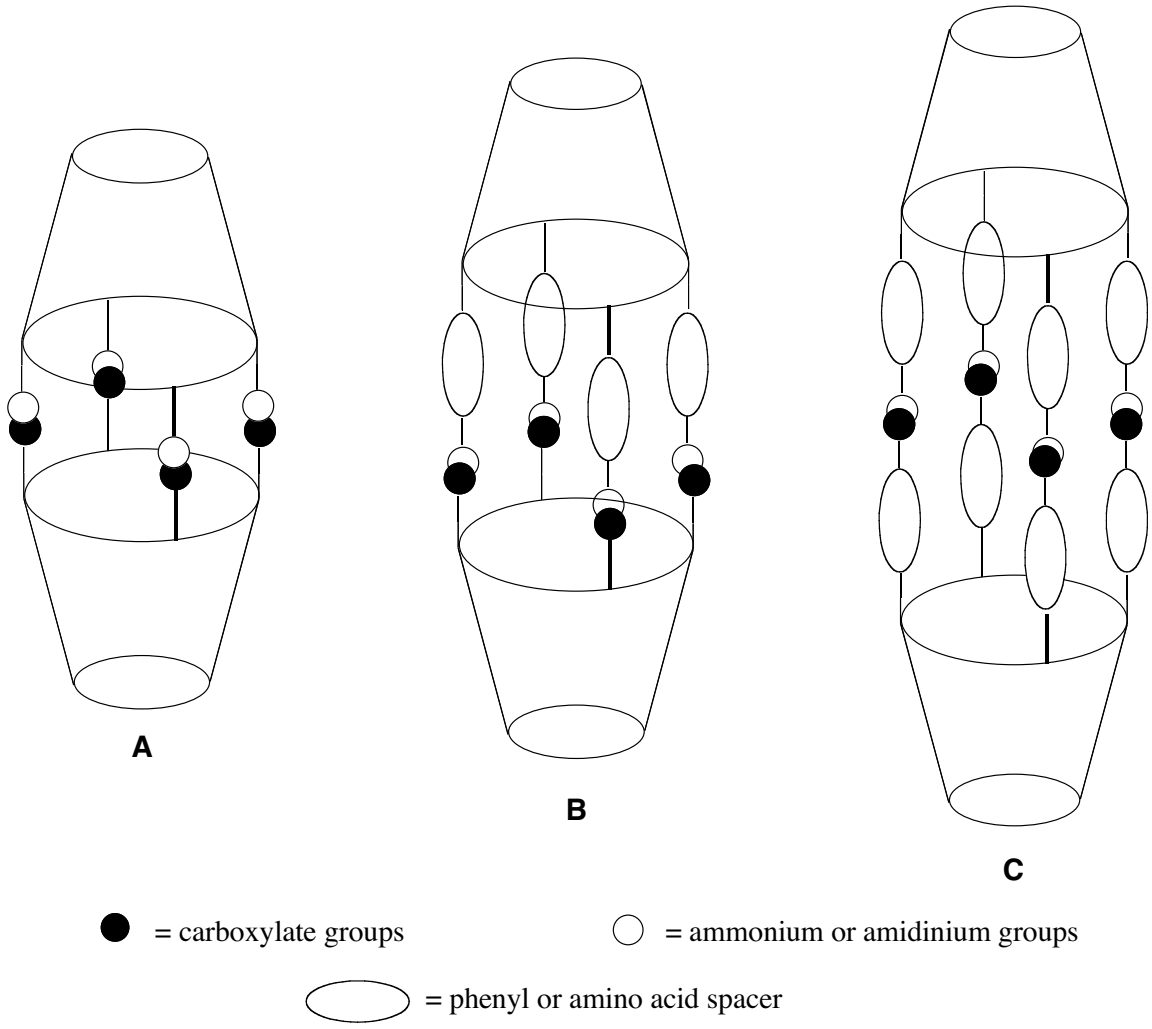
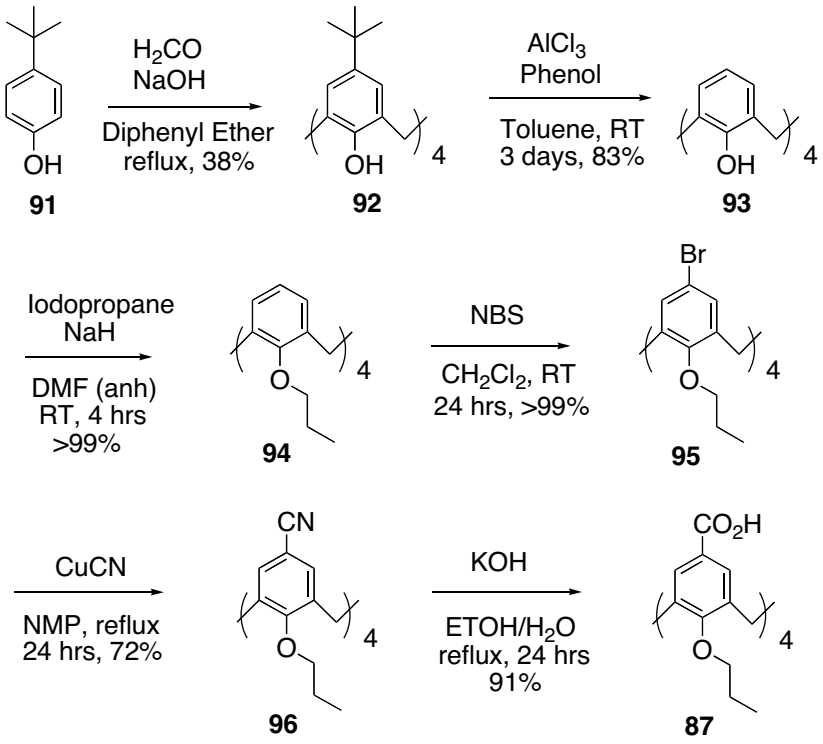


Figure 2-2. Calix[4]arene Heterodimer Structures

2.2.1 Carboxycalix[4]arene

Carboxycalix[4]arene (**87**) was synthesized in six steps from *t*-butyl phenol (**91**) (Scheme 2-1). *t*-Butyl calix[4]arene (**92**) was synthesized through a condensation reaction of *t*-butyl phenol (**91**) and formaldehyde.[26] The *t*-butyl groups were then removed using aluminum chloride and phenol in toluene.[26] Calix[4]arene (**93**) was then propylated using iodopropane and sodium hydride in anhydrous dimethylformamide.[27] Tetrapropoxycalix[4]arene (**94**) was brominated with *N*-bromosuccinamide in methylene

chloride to form the bromo derivative **95**. Bromocalix[4]arene (**95**) was converted into nitrilocalix[4]arene (**96**) through the Rosenmund von Braun reaction.[28] The nitrile was then hydrolyzed with potassium hydroxide in ethanol/water to form carboxycalix[4]arene (**87**).



Scheme 2-1. Synthesis of Carboxycalix[4]arene **87**

The self-assembly of carboxycalix[4]arene (**87**) with *C*-linked-alaninocalix[4]arene (**84**) or anilinocalix[4]arene (**86**) was studied by ^{1}H NMR dilution studies and Job Plots in DMSO-d_6/5% aqueous phosphate buffer. ^{1}H NMR dilution studies indicate that anilinocalix[4]arene (**86**) and carboxycalix[4]arene (**87**) do not dimerize in the DMSO-d_6/5% phosphate buffer at pH 4.3. The lack of assembly is shown

in the Job Plot of **86** and **87** (Figure 2-3) by the erratic points that do not have a maximum. A maximum at 0.5 would indicate assembly with a 1:1 ratio of monomers.

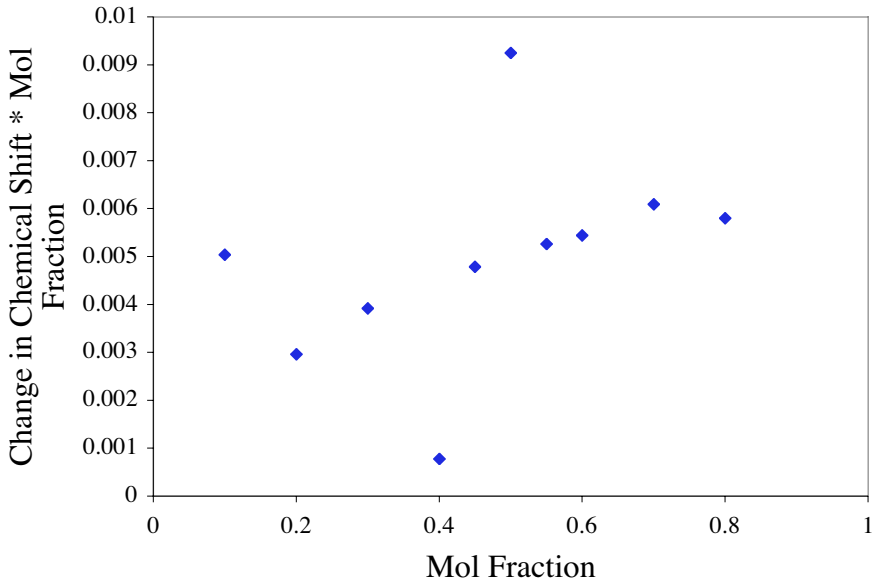


Figure 2-3. Job Plot of Carboxycalix[4]arene **87** and Anilinocalix[4]arene **86**

Carboxycalix[4]arene (**87**) and *C*-linked-alaninocalix[4]arene (**84**) were found to dimerize in DMSO-d_6/5% phosphate buffer at pH 6.5. The association constant (K_a) of dimer **84:87** was calculated to be 1200 M^{-1} using Equation 1.[29]

$$\frac{[B_0]}{(\partial_{obs} - \partial_a)} = \frac{1}{(\partial_c - \partial_a)}([A_0] + [B_0] - [C_0]) + \frac{1}{K_c(\partial_c - \partial_a)} \quad \text{Equation 1}$$

where $[B_0]$ = the initial concentration of monomer B, $[A_0]$ = the initial concentration of monomer A, $[C_0]$ = the dimer concentration, ∂_{obs} = the observed chemical shift, ∂_a = the

chemical shift of monomer A, ∂_c = the chemical shift of the dimer, and K_c = the association constant.

A graph of the change in chemical shift of the aromatic protons of *C*-linked-alaninocalix[4]arene (**84**) *versus* concentration as a monomer and as a dimer with carboxycalix[4]arene (**87**) is shown in Figure 2-4. The chemical shift of the aromatic protons of the monomer alone does not change upon dilution. Upon dilution of the dimer, the chemical shift increases towards that of the monomer. This indicates the presence of a dimer at higher concentrations and the monomers at lower concentrations. The Job Plot of **84** and **87** has a maximum at 0.5 that indicates the formation of a supramolecular structure with a 1:1 ratio of the monomers (Figure 2-5). Anilinocalix[4]arene (**86**) did not dimerize with carboxycalix[4]arene (**87**) due to the small difference in pK_a between the terminal amine of **86** (pK_a ~4.7) and the acid of **87** (pK_a ~4.2). Carboxycalix[4]arene (**87**, pK_a ~4.2) did dimerize with *C*-linked-alaninocalix[4]arene (**84**, pK_a ~9) due to the larger difference in pK_a's between the associating functionalities of the monomers.

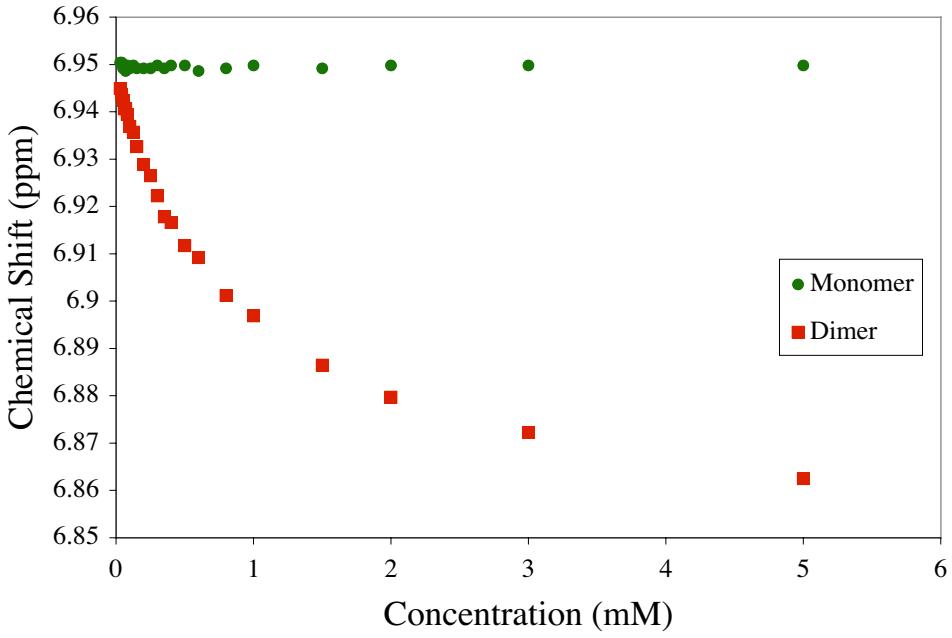


Figure 2-4. Change in Chemical Shift of the Aromatic Protons of *C*-Linked-Alaninocalix[4]arene **84** vs. Concentration as a Monomer and as a Dimer with Carboxycalix[4]arene **87**

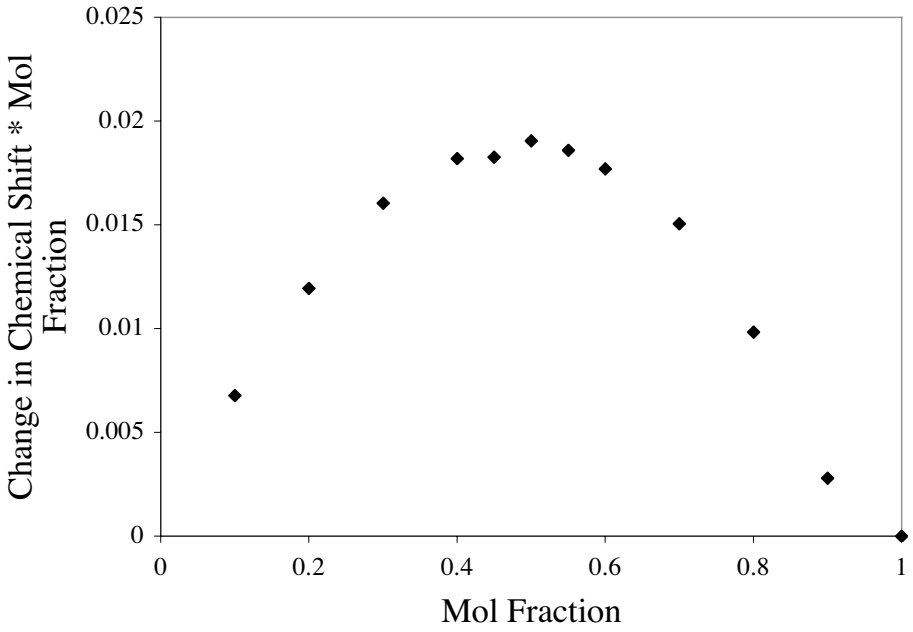
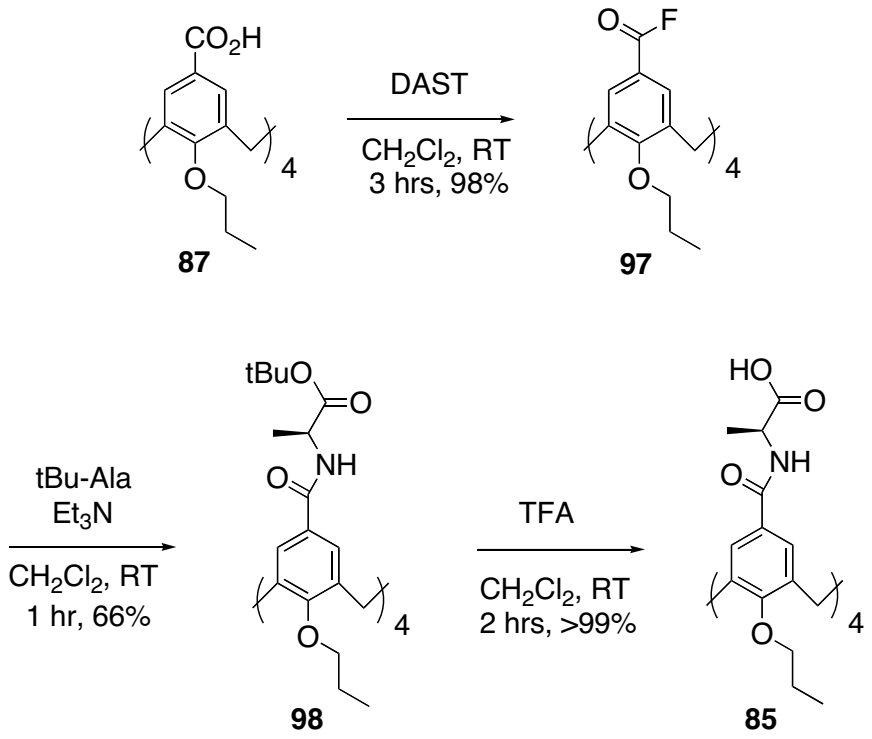


Figure 2-5. Job Plot of Carboxycalix[4]arene **87** and *C*-Linked-Alaninocalix[4]arene **84**

2.2.2 *N*-Linked-alaninocalix[4]arene

N-linked-alaninocalix[4]arene (**85**) was synthesized in three steps from carboxycalix[4]arene (**87**) (Scheme 2-2). Carboxycalix[4]arene (**87**) was converted to the acid fluoride **97** using diethylaminosulfur trifluoride (DAST) in methylene chloride.[30] *t*-Butyl protected alanine was then coupled to **97** using triethylamine in methylene chloride to form *t*-butyl-protected alaninocalix[4]arene (**98**). Deprotection of **98** with trifluoroacetic acid (TFA) in methylene chloride affords the desired product, *N*-linked-alaninocalix[4]arene (**85**).



Scheme 2-2. Synthesis of *N*-linked-Alaninocalix[4]arene **85**

The self-assembly of *N*-linked-alaninocalix[4]arene (**85**) with *C*-linked-alaninocalix[4]arene (**84**) or anilinocalix[4]arene (**86**) into heterodimers was studied by

^{1}H NMR in DMSO-d_6/5% aqueous phosphate buffer. Anilinocalix[4]arene (**86**) did not dimerize with *N*-linked-alaninocalix[4]arene (**85**) in DMSO-d_6/5% phosphate buffer at pH 4.3. The chemical shift of the beta protons of **85** from the monomer dilution study are subtracted by the chemical shift of the beta protons of **85** from the dimer dilution study and plotted *versus* concentration (Figure 2-6) to show the lack of dimerization. This plot shows an almost linear line near zero indicating that indicated that the chemical shift of the alanine derivative's beta protons is the same with or without the addition of anilinocalix[4]arene (**86**). A Job Plot of *N*-linked-alaninocalix[4]arene (**85**) and anilinocalix[4]arene (**86**) is shown in Figure 2-7. The lack of assembly is shown in the Job Plot by the erratic points that do not have a maximum.

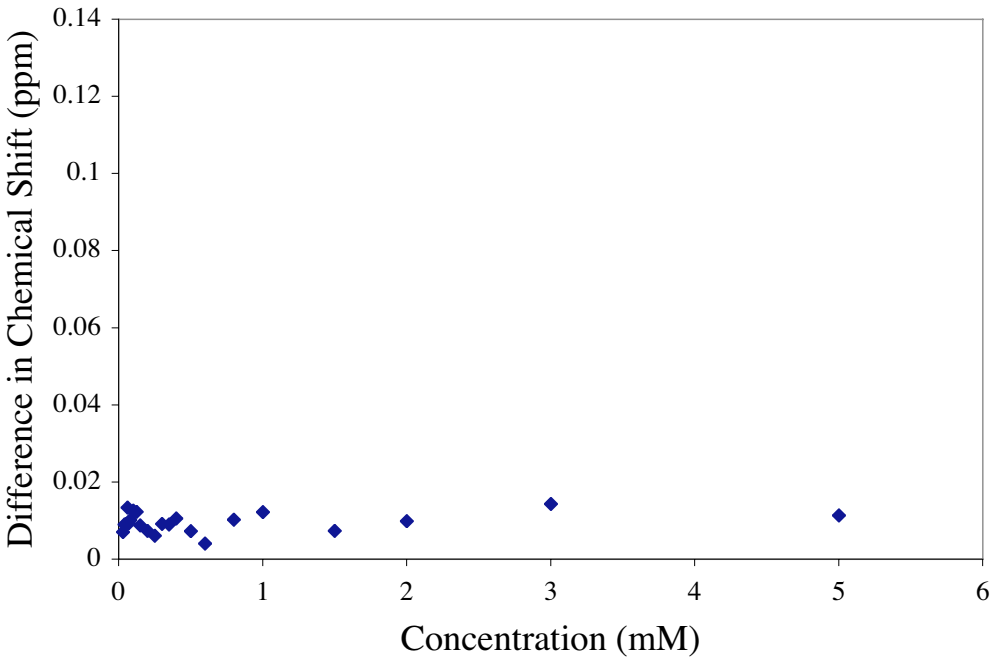


Figure 2-6. Subtraction of the Chemical Shift of the Beta Protons from Dilution Studies of *N*-Linked-Alaninocalix[4]arene **85** Alone and as a Dimer with Anilinocalix[4]arene **86**

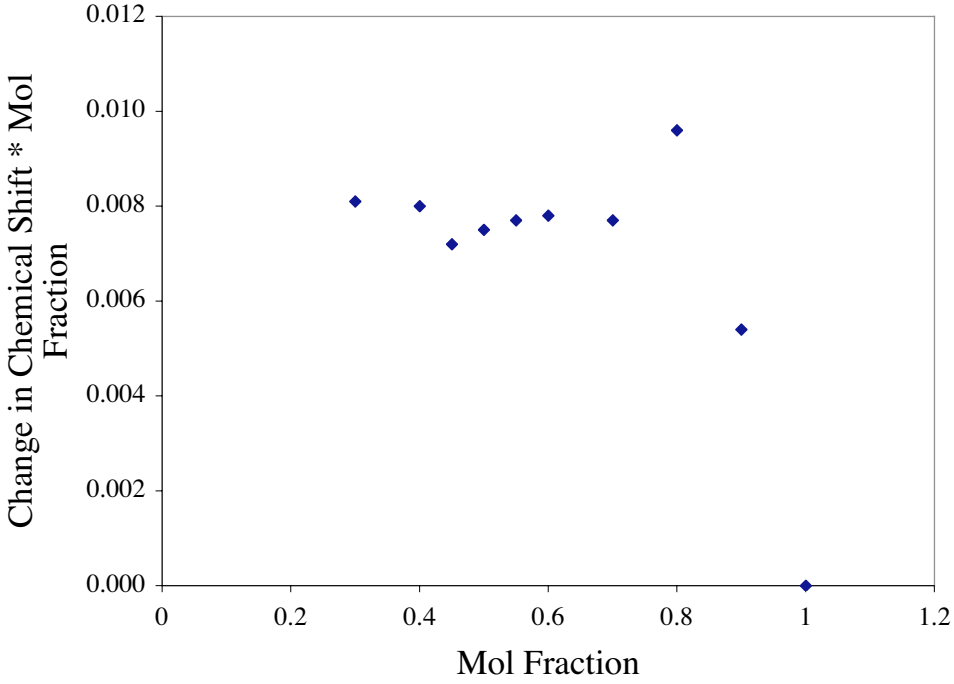


Figure 2-7. Job Plot of *N*-Linked-Alaninocalix[4]arene **85** and Anilinocalix[4]arene **86**

N-linked-alaninocalix[4]arene (**85**) and *C*-linked-alaninocalix[4]arene (**84**) were found to dimerize in DMSO-d_6/5% phosphate buffer at pH 6.5. The association constant (K_a) of dimer **84:85** was calculated to be 5040 M^{-1} (Equation 1).[29] Figure 2-8 is a plot of the subtraction of the chemical shift of the beta protons of **85** alone from the chemical shift of the beta protons of **85** from the dimer dilution study *versus* concentration. The difference in chemical shifts decreases as the dimer is diluted indicating a shift from dimer at higher concentrations to monomers at lower concentrations. Figure 2-9 is a graph of the change in chemical shift of the aromatic protons of *C*-linked-alaninocalix[4]arene (**84**) *versus* concentration as a monomer and as a dimer with *N*-linked-alaninocalix[4]arene (**85**). The chemical shift, of the monomer aromatic protons, does not change upon dilution. As the dimer is diluted, the chemical shift increases

towards that of the monomer. This shift indicates the presence of a dimer at higher concentrations and monomers at lower concentrations. The Job Plot of **84** and **85** has a maximum at 0.5 that indicates the formation of a supramolecular structure with a 1:1 ratio of monomers (Figure 2-10). Anilinocalix[4]arene (**86**) did not dimerize with *N*-linked-alaninocalix[4]arene (**85**) due to the small difference in pK_a between it (pK_a ~4.7) and **85** (pK_a ~2.4). *N*-linked-alaninocalix[4]arene (**85**, pK_a ~2.4) did dimerize with *C*-linked-alaninocalix[4]arene (**84**, pK_a ~9) due to the larger difference in pK_a's.

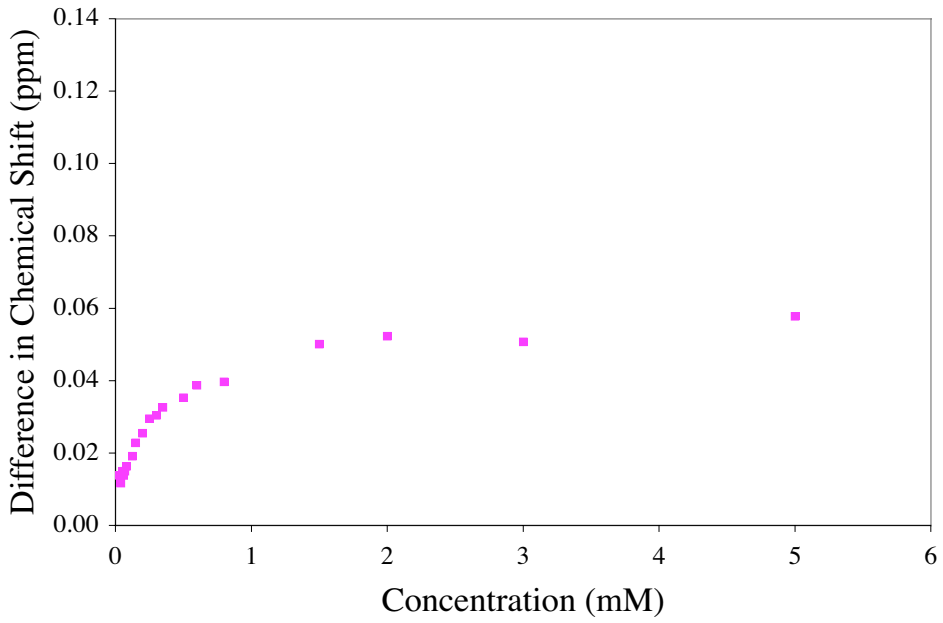


Figure 2-8. Subtraction of the Chemical Shift of the Beta Protons from Dilution Studies of *N*-Linked-Alaninocalix[4]arene **85** as a Monomer and Dimer with *C*-Linked-Alaninocalix[4]arene **84**

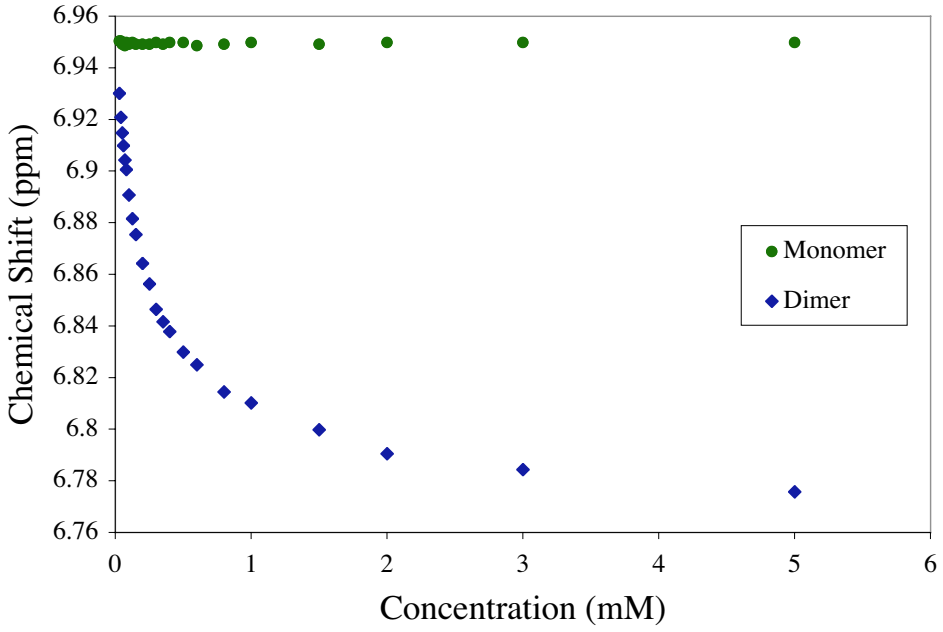


Figure 2-9. Chemical Shift of the Aromatic Protons of *C*-Linked-Alaninocalix[4]arene **84** vs. Concentration as a Monomer and as a Dimer with *N*-Linked-Alaninocalix[4]arene **85**

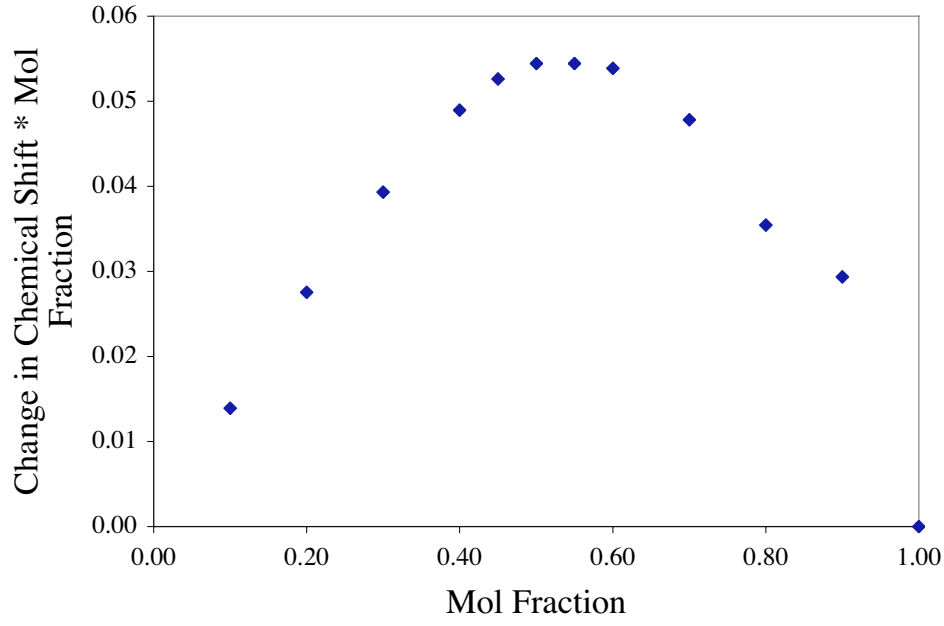
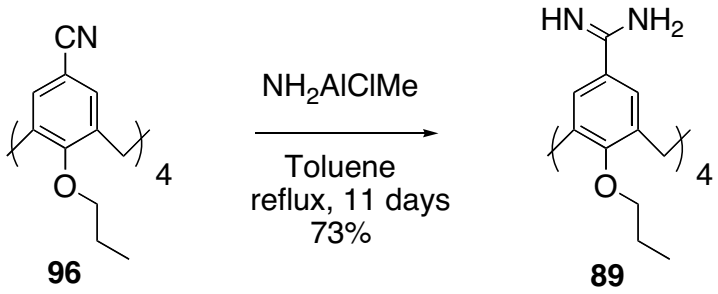


Figure 2-10. Job Plot of *C*-Linked-Alaninocalix[4]arene **84** and *N*-Linked-Alaninocalix[4]arene **85**

2.2.3 Amidinocalix[4]arene

Amidinocalix[4]arene (**89**) was synthesized from nitrilocalix[4]arene (**96**) in one step using an alkylchloroaluminum amide (Scheme 2-3). The aluminum reagent was prepared *in situ* from trimethyl aluminum and ammonium chloride in dichloroethane.[31]



Scheme 2-3. Synthesis of Amidinocalix[4]arene **89**

No dimerization was observed in the dilution studies or Job Plots of amidinocalix[4]arene (**89**) with carboxycalix[4]arene (**87**) in DMSO-d_6/5% phosphate buffer at pH 8.8. The lack of assembly is shown by graphing the chemical shifts of the aromatic protons of **87** from the monomer dilution study are subtracted by the chemical shift of the aromatic protons of **87** from the dimer dilution study *versus* concentration (Figure 2-11). The plot of the subtracted chemical shifts stays around zero, which indicates that the chemical shift of the acid derivative's aromatic peaks is the same with or without the addition of amidinocalix[4]arene (**89**). The lack of dimerization is also shown in the erratic Job Plot that lacks a maximum (Figure 2-12). Dilution studies of amidinocalix[4]arene (**89**) and *N*-linked-alaninocalix[4]arene (**85**) in CD_3OD/5% phosphate buffer at pH 8.8 are inconclusive. The Job Plot shows the formation of a dimer

with a 1:1 ratio of monomers but the ^{1}H NMR dilution studies do not show dimer formation.

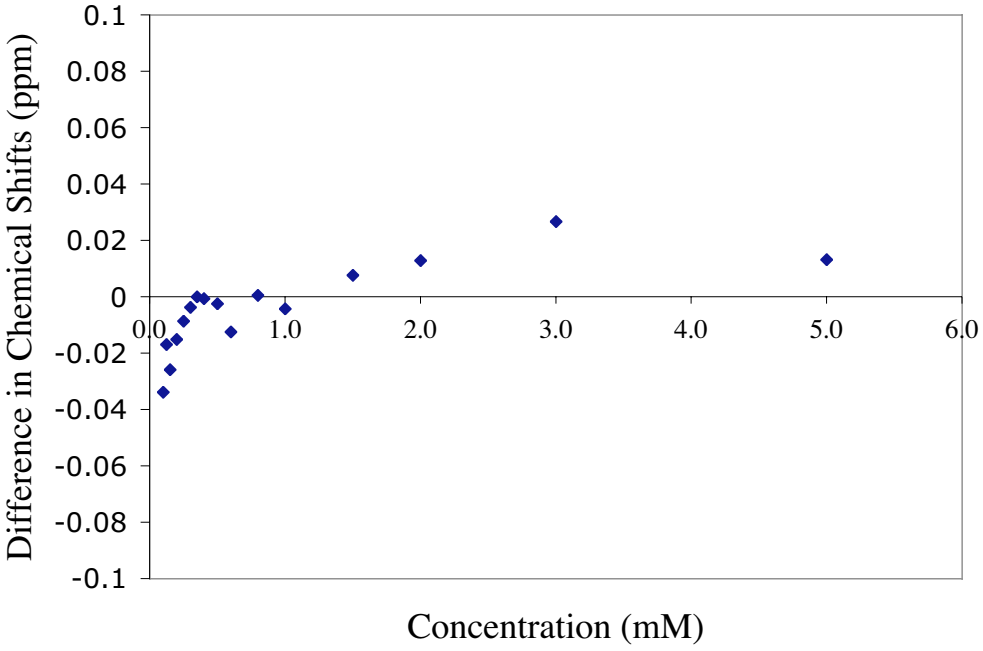


Figure 2-11. Subtraction of the Chemical Shift of the Aromatic Protons from Dilution Studies of Carboxycalix[4]arene **87** as a Monomer and Dimer with Amidinocalix[4]arene **89**

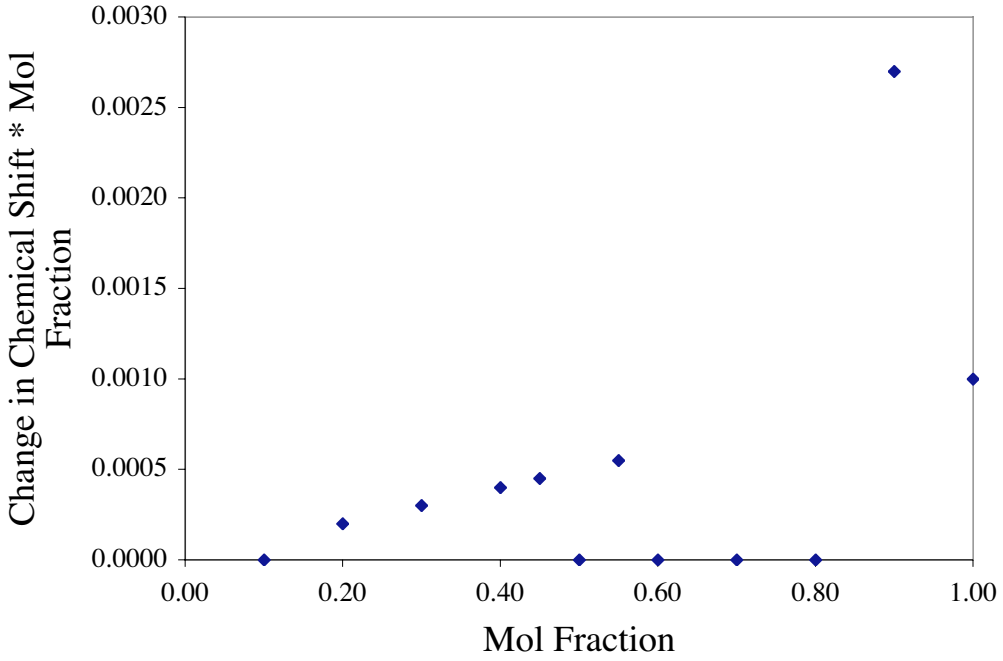
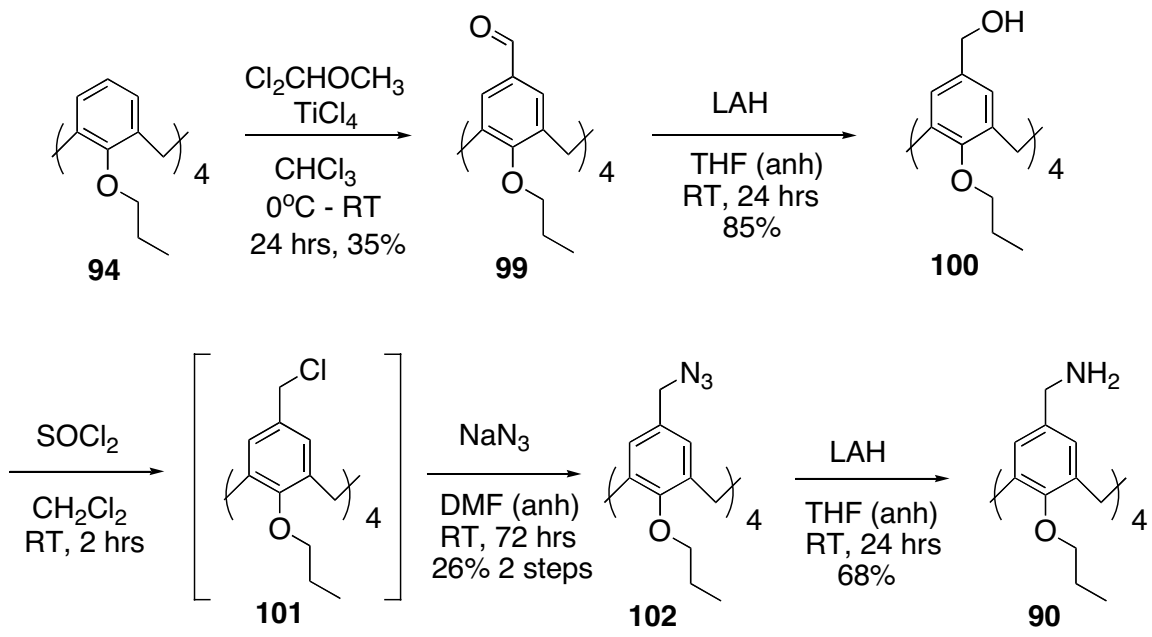


Figure 2-12. Job Plot of Amidinocalix[4]arene **89** and Carboxycalix[4]arene **87**

2.2.4 Aminomethylcalix[4]arene

Aminomethylcalix[4]arene (**90**) was synthesized from tetrapropoxycalix[4]arene (**94**) in 5 steps (Scheme 2-4). Tetrapropoxycalix[4]arene (**94**) was formylated using 1,1-dichlorodimethyl ether and titanium chloride.[32] The tetraformylated derivative **99** was then reduced with lithium aluminum hydride to hydroxymethylcalix[4]arene (**100**). The hydroxy group was substituted with a chloride using thionyl chloride,[33] which was then displaced with an azide to form azidomethylcalix[4]arene (**102**). The azide was then reduced with lithium aluminum hydride to afford the desired product, aminomethylcalix[4]arene (**90**).[34] Dimerization studies of aminomethylcalix[4]arene (**90**) and *N*-linked alaninocalix[4]arene (**85**) were attempted in DMSO-d_6 with 5% phosphate buffer (pH 4.3) but **90** was not soluble in this solvent system.



Scheme 2-4. Synthesis of Aminomethylcalix[4]arene **90**

2.2.5 Heterodimer Results

The ability of calix[4]arene derivatives to self-assemble into capsules in polar solvents has been demonstrated. *C*-linked-alaninocalix[4]arene (**84**) dimerizes with *N*-linked-alaninocalix[4]arene (**85**), carboxycalix[4]arene (**87**), and carboxyphenylcalix[4]arene (**88**) in the DMSO-d_6/5% phosphate buffer at pH 6.5 as shown in Figure 2-13. The monomers with the largest pK_a difference formed the strongest dimer **84:85** (K_a = 5040 M^{-1}) followed by **84:88** (K_a = 4410 M^{-1}) and **84:87** (K_a = 1200 M^{-1}). It is interesting to note that addition of the phenyl spacers to the calix[4]arene scaffold increases the size of the capsule with little effect on its ability to dimerize.

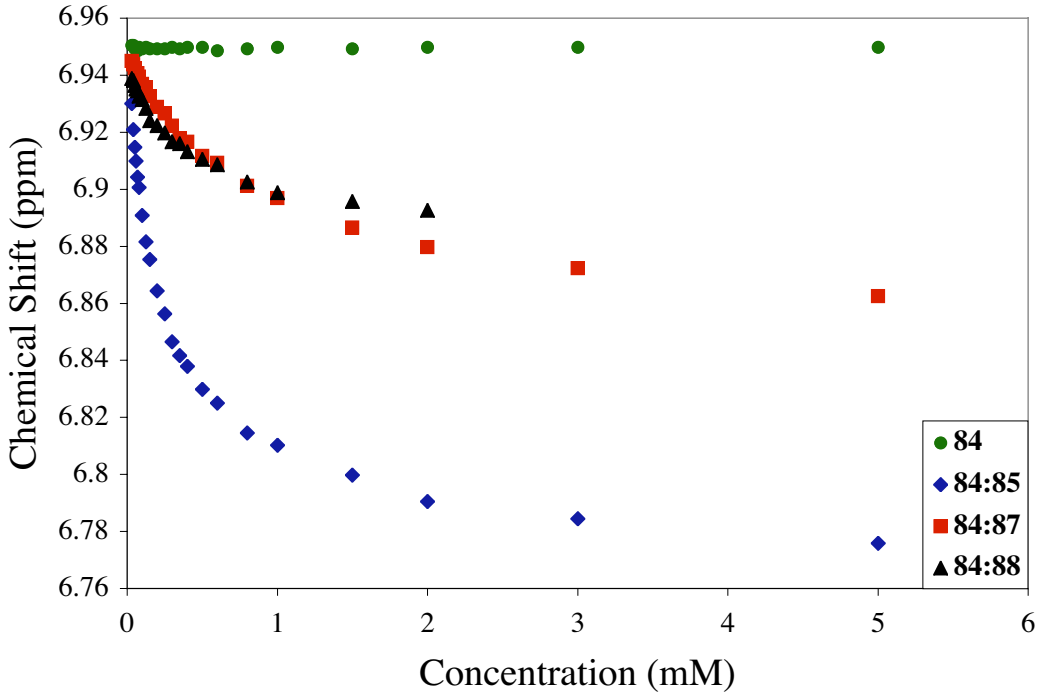


Figure 2-13. Comparison of the Dilution Studies of the Monomer **84** with all of the Heterodimers Formed (**84**:**85**, **84**:**87**, and **84**:**88**)

2.3 Calix[4]arene Homodimers

Several calix[4]arene derivatives propylated on the lower rim and disubstituted with ionic functional groups on the upper rim have been synthesized. These derivatives are dicarboxydiglycinocalix[4]arene (**103**), dialaninodicarboxycalix[4]arene (**104**), di-ß-alaninodicarboxycalix[4]arene (**105**), and di-γ-aminobutyric acid dicarboxycalix[4]arene (**106**) (Figure 2-14). Dialaninodicarboxycalix[4]arene (**104**) was synthesized and studied by Dr. Beth Brewster.

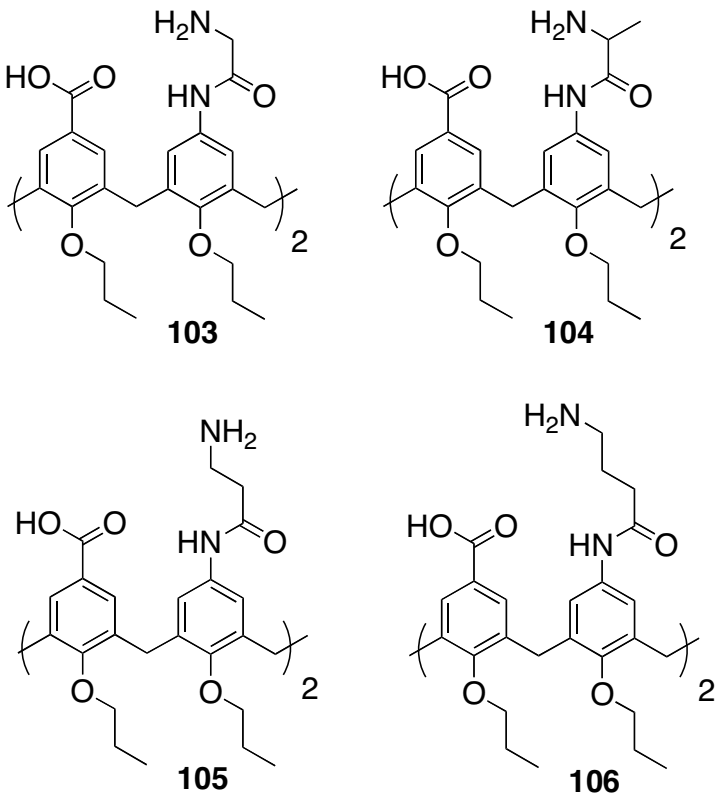


Figure 2-14. Calix[4]arene Homodimer Derivatives

All of the derivatives were studied for their ability to self-assemble into interdigitated homodimers by ^{1}H NMR dilution studies. The dilution studies were performed in 95% methanol-d_4 (CD_3OD) with 5% phosphate buffer (pH 6.5) or 5% deuterium oxide (D_2O). Figure 2-15 shows a cartoon of the dimerization. Job plots were not performed because they are only used for supramolecular assemblies containing heteromolecules. The ^{1}H NMR spectra from the dilution studies have sharp peaks that are consistent with the formation of small assemblies. Larger assemblies would have broader peaks. The amino acids used were chosen to determine if the chain length would have any effect on the association of the derivatives.

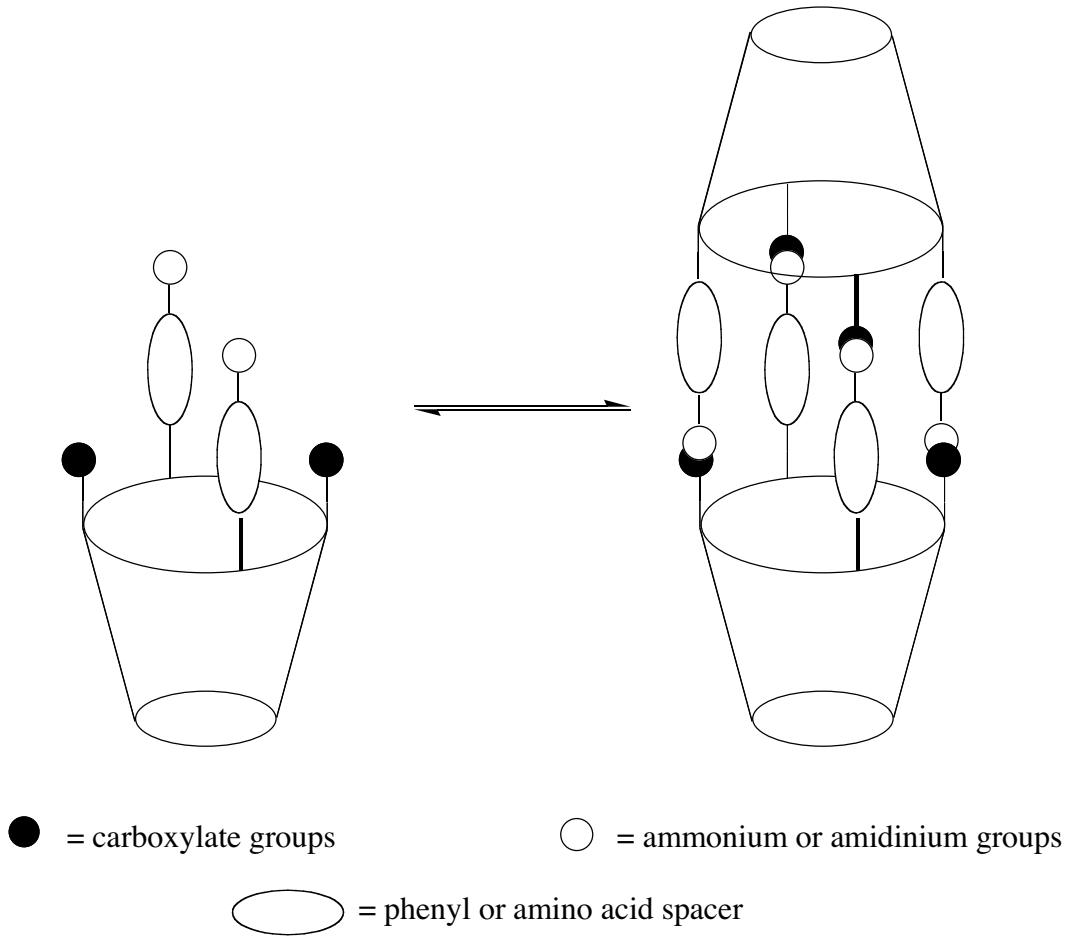
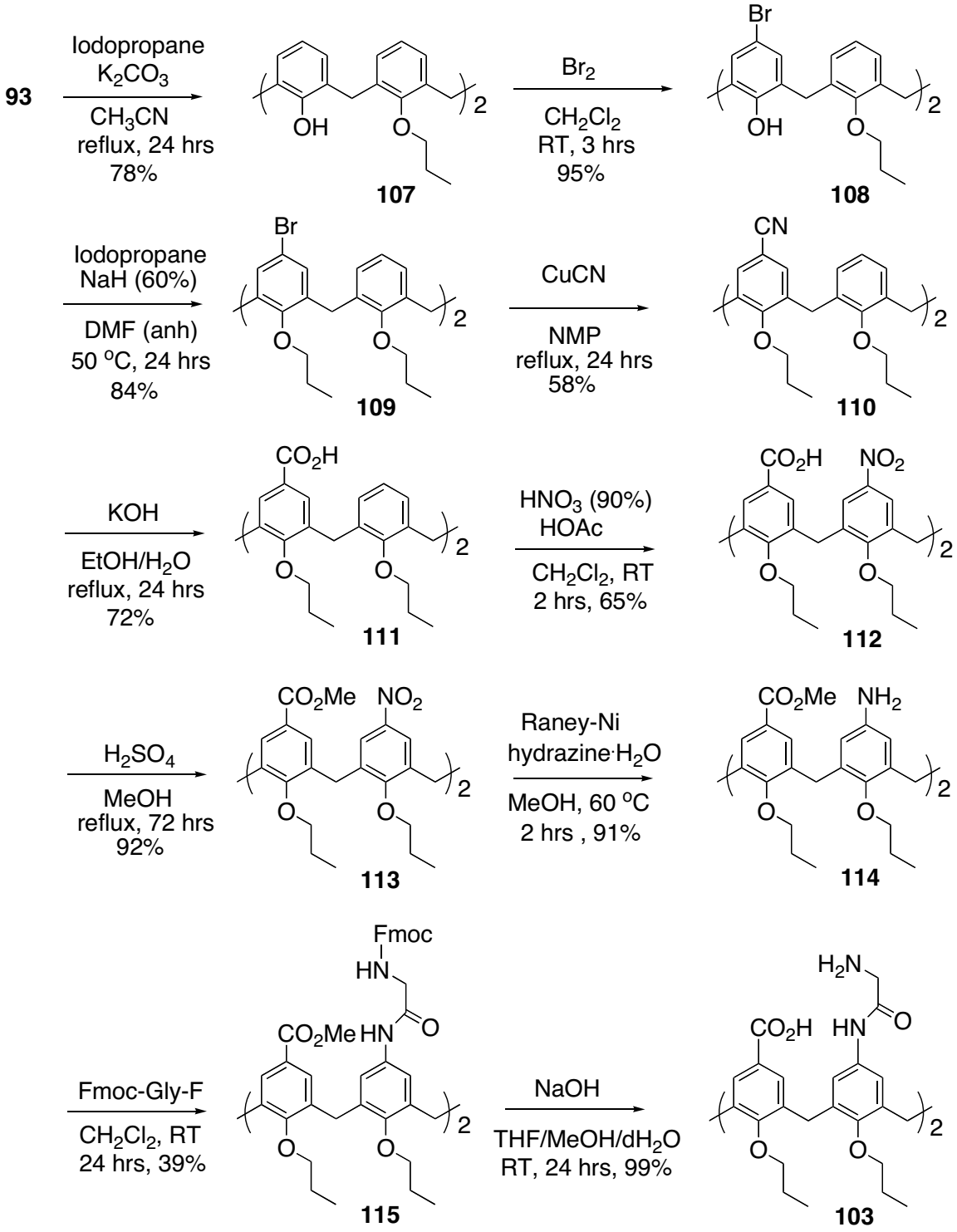


Figure 2-15. Interdigitated Calix[4]arene Homodimer Structures

2.3.1 Dicarboxydiglycinocalix[4]arene

Dicarboxydiglycinocalix[4]arene (**103**) was synthesized from *t*-butyl phenol (**91**, Scheme 2-1) in twelve steps (Scheme 2-5). Dihydroxydipropoxycalix[4]arene (**107**) was synthesized from calix[4]arene (**93**, Scheme 2-1) using potassium carbonate and iodopropane in acetonitrile.[35, 36] Dihydroxydipropoxycalix[4]arene (**107**) was brominated using bromine in methylene chloride to form dibromodihydroxydipropoxycalix[4]arene (**108**). The dibromo derivative **108** is formed exclusively due to the increased reactivity of the unsubstituted phenol rings over the alkylated phenol rings. The dibromo compound

108 was then exhaustively propylated with iodopropane and sodium hydride in anhydrous dimethyl formamide yielding dibromotetrapropoxycalix[4]arene (**109**). The bromines were converted into nitriles using the Rosenmund Von Braun reaction.[28] Dinitrilocalix[4]arene (**110**) was then hydrolyzed to dicarboxycalix[4]arene (**111**) using potassium hydroxide in ethanol/water. The diacid was nitrated using 90% nitric acid and glacial acetic acid in methanol to give dicarboxydinitrocalix[4]arene (**112**).[27] The acids were then converted into methyl esters using sulfuric acid in methanol. The nitro groups were then reduced with Raney-nickel and hydrazine monohydrate in methanol to afford dianilinodicarboxymethylcalix[4]arene (**114**).[27] *N*-(9-Fluorenylmethoxycarbonyl (Fmoc) protected glycine acid fluoride was coupled to **114** in methylene chloride. Deprotection of the methyl ester and Fmoc carbamate was achieved in one step using sodium hydroxide in a mixture of tetrahydrofuran, methanol, and water yielding the final product dicarboxydiglycinocalix[4]arene (**103**).



Scheme 2-5. Synthesis of Dicarboxydiglycinocalix[4]arene **103**

Proton NMR dilution studies were performed with dicarboxydiglycinocalix[4]arene (**103**) in 95% CD_3OD with either 5% phosphate buffer (pH 6.5) or 5% D_2O. Figure 2-16 shows the chemical shift of the aromatic protons of **103** *versus* the concentration. In CD_3OD with 5% phosphate buffer, the dilution curve is S-shaped. This S-shape represents the shift in equilibrium from a solution where the derivatives are mostly associating into dimers (high concentration) to a solution where the derivatives are predominately monomers (low concentration). The association constant (K_a) for **103** in CD_3OD with 5% phosphate buffer was calculated to be 497 M^{-1} using Equation 2.[37, 38]

$$\partial_{obs} = \partial_m + \left(\partial_d - \partial_m\right)\frac{\sqrt{1+8K\left[A_0\right]}-1}{\sqrt{1+8K\left[A_0\right]}+1} \qquad \text{Equation 2}$$

where ∂_{obs} = the observed chemical shift, ∂_m = the chemical shift of the monomer, ∂_d = the chemical shift of the dimer, K = the association constant, and $[A_0]$ = the initial concentration.

In CD_3OD with 5% D_2O, the curve starts out at ~7.2 ppm and starts to increase rapidly towards the chemical shift of the monomer (~7.75 ppm). The steep slope and the fact that the complexes never dissociates fully into monomers suggests that **103** forms very strong complexes in CD_3OD with 5% D_2O. The data from the dilution study of **103** in CD_3OD with 5% D_2O does not fit the equation for the determination of the association constant of a homodimer. While dicarboxydiglycinocalix[4]arene (**103**) is forming some

kind of aggregate in CD_3OD with 5% D_2O, the nature of the complex is still not fully understood.

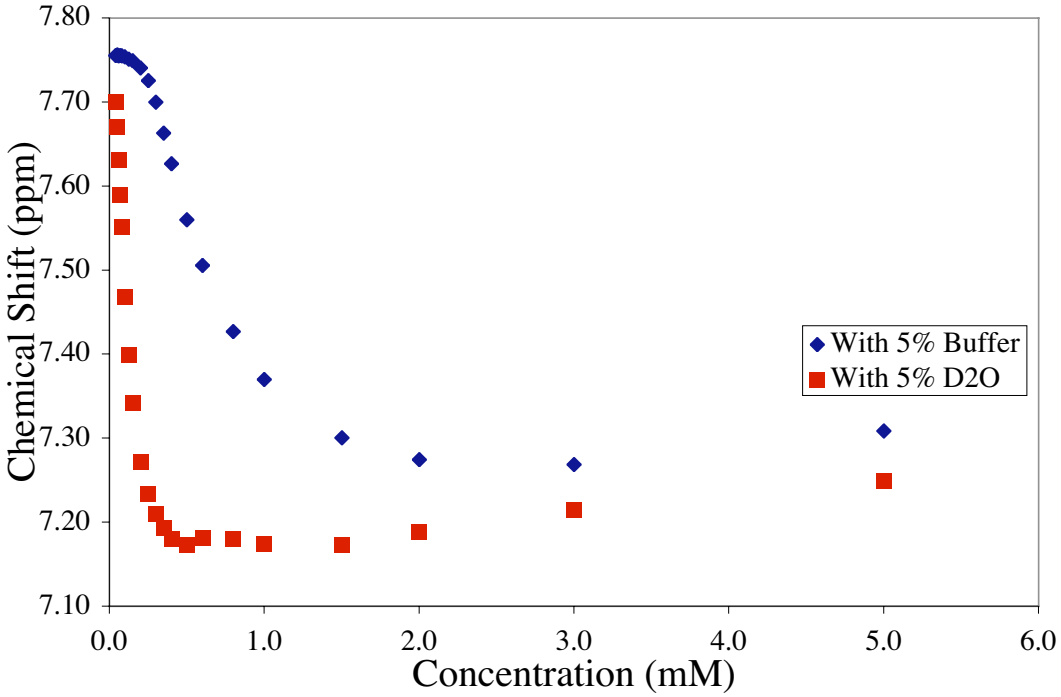
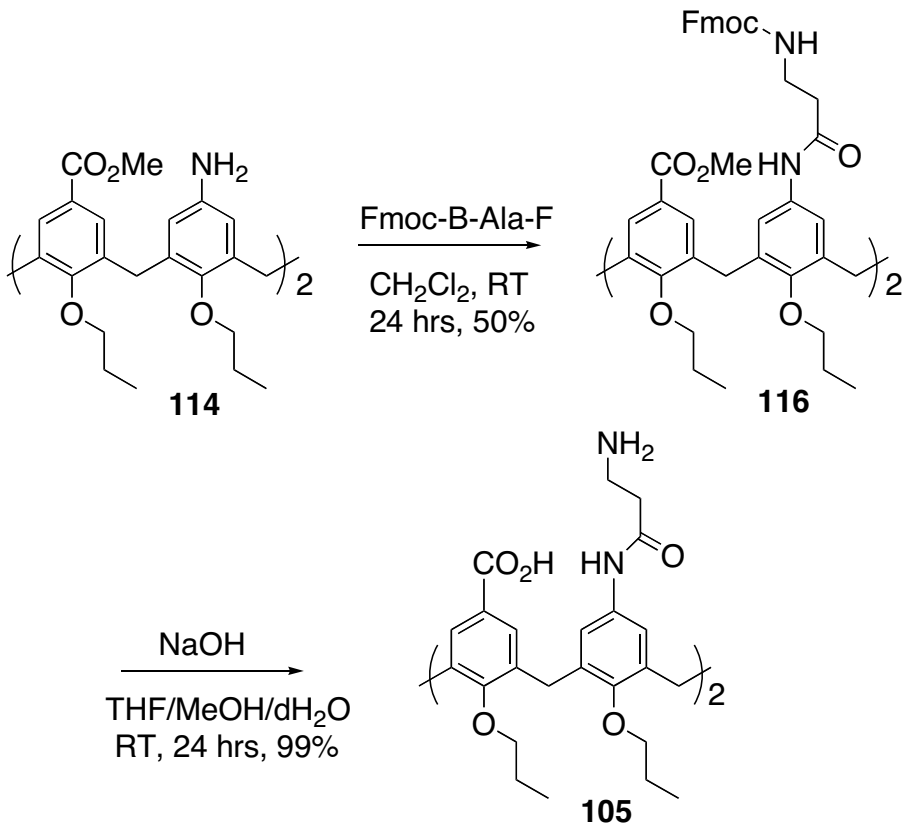


Figure 2-16. Dilution Study of Dicarboxydiglycinocalix[4]arene **103** in CD_3OD with 5% Phosphate Buffer or 5% D_2O

2.3.2 Di-β-alaninodicarboxycalix[4]arene

Di-β-alaninodicarboxycalix[4]arene (**105**) was synthesized from dianilinodicarboxymethylcalix[4]arene (**114**) (Scheme 2-6). Fmoc protected β-alanine acid fluoride was coupled to the calix[4]arene in methylene chloride. Deprotection of the methyl ester and Fmoc carbamate was achieved in one step using sodium hydroxide in a mixture of tetrahydrofuran, methanol, and water yielding the final product di-β-alaninodicarboxycalix[4]arene (**105**).



Scheme 2-6. Synthesis of Di-β-alaninodicarboxycalix[4]arene **105**

Proton NMR dilution studies were performed with di-β-alaninodicarboxycalix[4]arene (**105**) in 95% CD_3OD with either 5% phosphate buffer (pH 6.5) or 5% D_2O (Figure 2-17). The results of the dilution studies were very similar to the dilution studies of dicarboxydiglycinocalix[4]arene (**103**). In CD_3OD with 5% phosphate buffer, the dilution gave an S-shaped curve representing the shift in equilibrium from dimers (higher concentrations) to predominately monomers (lower concentrations). The association constant (K_a) for **105** in CD_3OD with 5% phosphate buffer was calculated to be 430 M^{-1} (Equation 2).[37, 38] In CD_3OD with 5% D_2O, the curve starts out at ~7.2 ppm and starts to increase rapidly towards the chemical shift of the monomer (~7.75 ppm). The fact that the complex never dissociates fully into monomers

along with the steep slope suggest that **105** forms stronger complexes in CD_3OD with 5% D_2O than in CD_3OD with 5% phosphate bufer. The data from the dilution study of **105** in CD_3OD with 5% D_2O does not fit the equation for the determination of the association constant of a homodimer. The nature of the complex of **105** in CD_3OD with 5% D_2O is not fully understood.

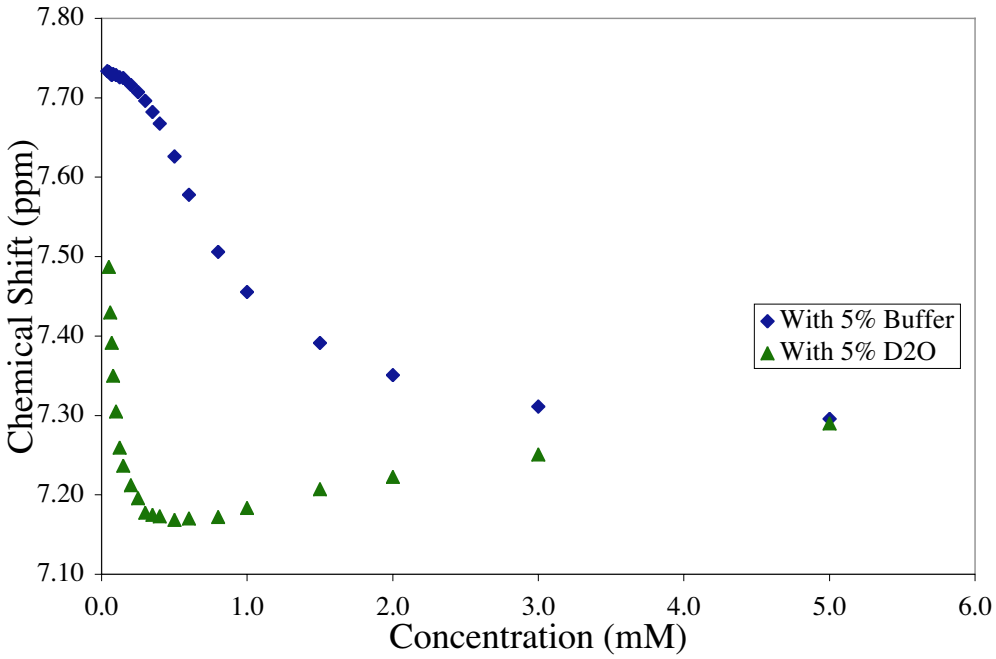
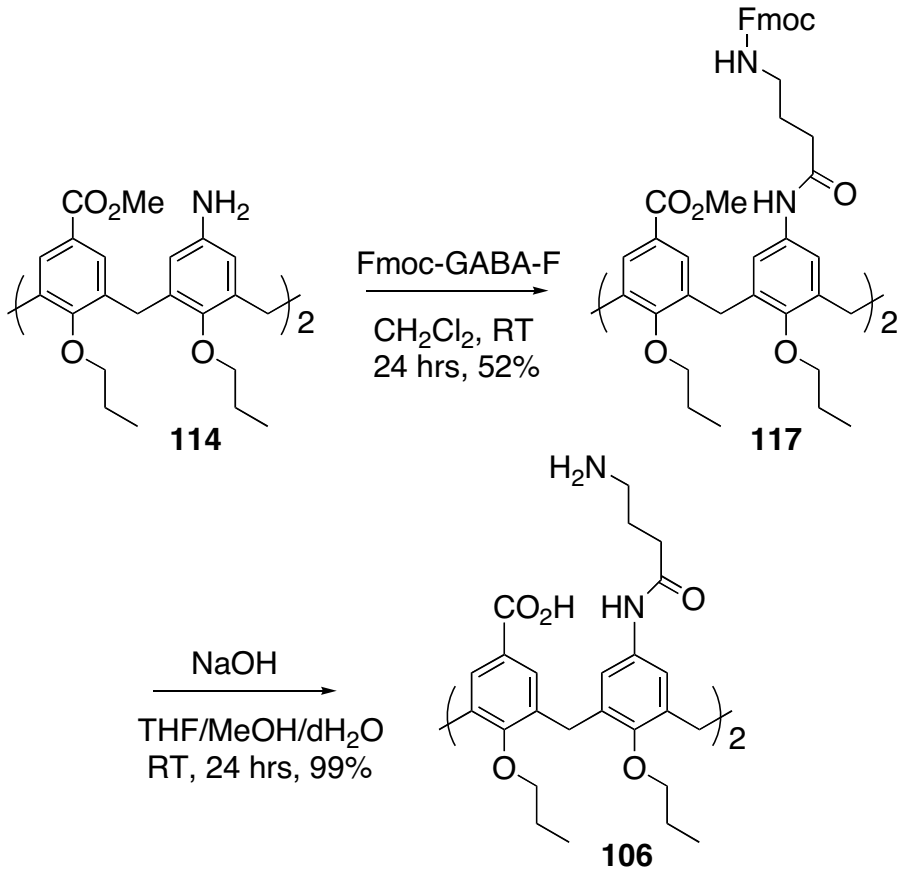


Figure 2-17. Dilution Study of Di-β-alaninodicarboxycalix[4]arene **105** in CD_3OD with 5% Phosphate Buffer or 5% D_2O

2.3.3 Di-γ-aminobutyric acid dicarboxycalix[4]arene

Di-γ-aminobutyric acid dicarboxycalix[4]arene (**106**) was synthesized from dianilinodicarboxymethylcalix[4]arene (**114**) (Scheme 2-7). Fmoc protected γ-aminobutyric acid fluoride was coupled to the calix[4]arene in methylene chloride. Deprotection of the methyl ester and Fmoc carbamate was achieved in one step using

sodium hydroxide in a mixture of tetrahydrofuran, methanol, and water yielding the final product di-γ-aminobutyric acid dicarboxycalix[4]arene (**106**).



Scheme 2-7. Synthesis of Di-γ-aminobutyric Acid Dicarboxycalix[4]arene **106**

Figure 2-18 shows the chemical shift of the aromatic protons of di-γ-aminobutyric acid dicarboxycalix[4]arene (**106**) *versus* the concentration from the ^{1}H NMR dilution studies in CD_3OD with either 5% phosphate buffer (pH 6.5) or 5% D_2O. The results of the dilution studies were very similar to the dilution studies of dicarboxydiglycinocalix[4]arene (**103**) and di-β-alaninodicarboxycalix[4]arene (**105**). In CD_3OD with 5% phosphate buffer, the dilution gave an S-shaped curve representing the

shift in equilibrium from dimers (higher concentrations) to predominately monomers (lower concentrations). The association constant (K_a) for **106** in CD_3OD with 5% phosphate buffer was calculated to be 180 M^{-1} (Equation 2).[37, 38] In CD_3OD with 5% D_2O, the curve starts out at ~7.25 ppm where the derivatives are mostly complexes and starts to increase rapidly towards the chemical shift of the monomer (~7.7 ppm). The formation of strong aggregates by **106** in CD_3OD with 5% D_2O is suggested by the steep slope of the graph. The data from the dilution study of **106** in CD_3OD with 5% D_2O does not fit the equation for the determination of the association constant of a homodimer. The nature of the aggregates formed from di-γ-aminobutyric acid dicarboxycalix[4]arene (**106**) in CD_3OD with 5% D_2O is not fully understood.

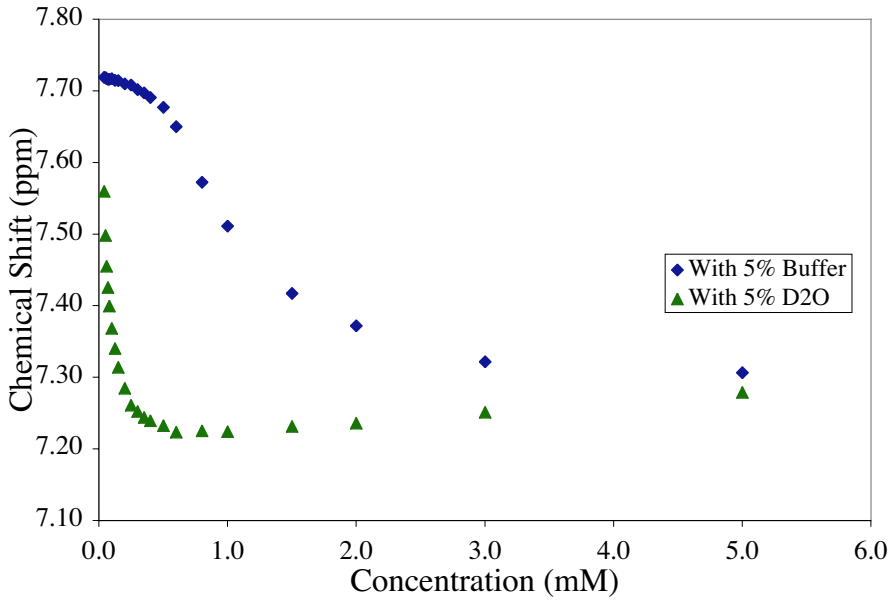


Figure 2-18. Dilution Study of Di-γ-aminobutyric Acid Dicarboxycalix[4]arene **106** in CD_3OD with 5% Phosphate Buffer or 5% D_2O

2.3.4 Interdigitated Homodimer Results

All of the calix[4]arene derivatives were studied by ^{1}H NMR for their ability to form interdigitated homodimers in methanol-d_4/5% D_2O and methanol-d_4/5% aqueous phosphate buffer at pH 6.5. All of the derivatives have similar association curves upon dilution. The strongest dimer in the CD_3OD with 5% phosphate buffer solution is the alanine derivative **104** (K_a = 700 M^{-1}), which was synthesized and studied by Dr. Beth Brewster. The second strongest dimer is the glycine derivative **103** K_a = (497 M^{-1}), followed by the β-alanine derivative **105** (K_a = 430 M^{-1}), and the γ-aminobutyric acid derivative **106** (K_a = 180 M^{-1}) (Figure 2-19). Increasing the chain length of the amino acid weaked the binding strength of the dimer in the CD_3OD/phosphate buffer solution. This weakening of the association strength might be due to the increased flexibility of the longer chains.

In the CD_3OD with 5% D_2O solution, di-β-alaninodicarboxycalix[4]arene (**105**) forms the strongest complex followed closely by di-γ-aminobutyric acid dicarboxycalix[4]arene (**106**), diglycinodicarboxycalix[4]arene (**103**), and last dialaninodicarboxycalix[4]arene (**104**) (Figure 2-20). While the derivatives do associate into complexes in 95% deuterated methanol with 5% deuterium oxide, they do not form dimers. The true nature of the complexes is still not fully understood. The chain length of the amino acid does not seem to have an affect in the association of the derivatives in the CD_3OD/D_2O solution suggested that the derivatives are associating in a different way than the dimers formed in the CD_3OD/phosphate buffer solution.

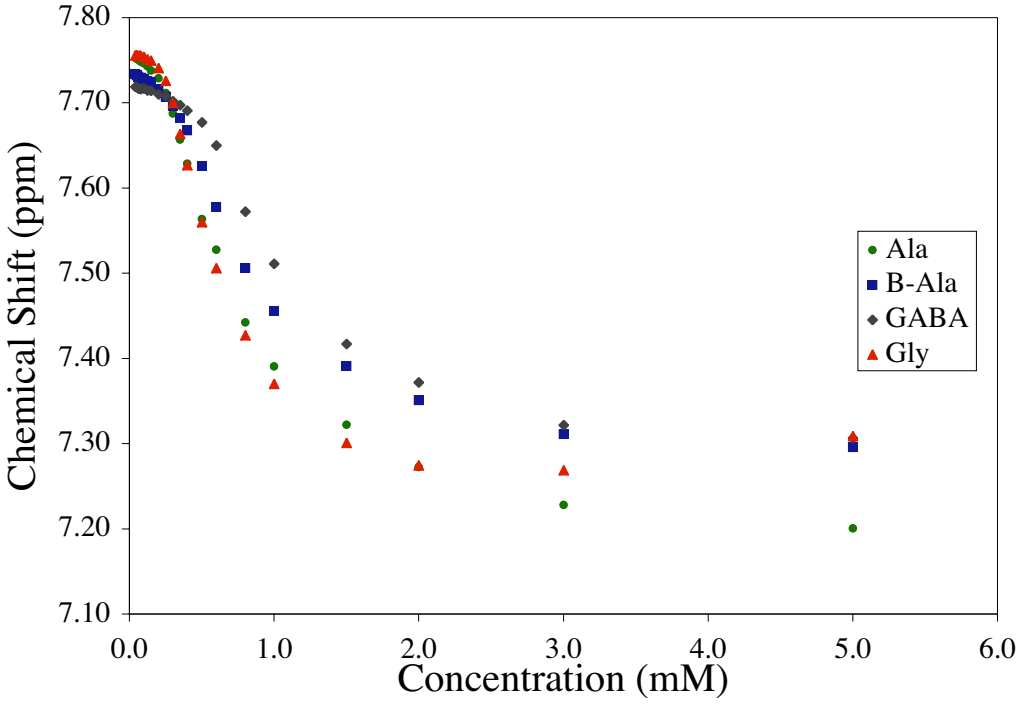


Figure 2-19. Dilution Studies of Interdigitated Homodimers in CD_3OD with 5% Phosphate Buffer (Ala = dialaninodicarboxycalix[4]arene **104**; B-Ala = di-β-alaninodicarboxycalix[4]arene **105**; GABA = di-γ-aminobutyric acid dicarboxycalix[4]arene **106**; Gly = dicarboxydiglycinocalix[4]arene **103**)

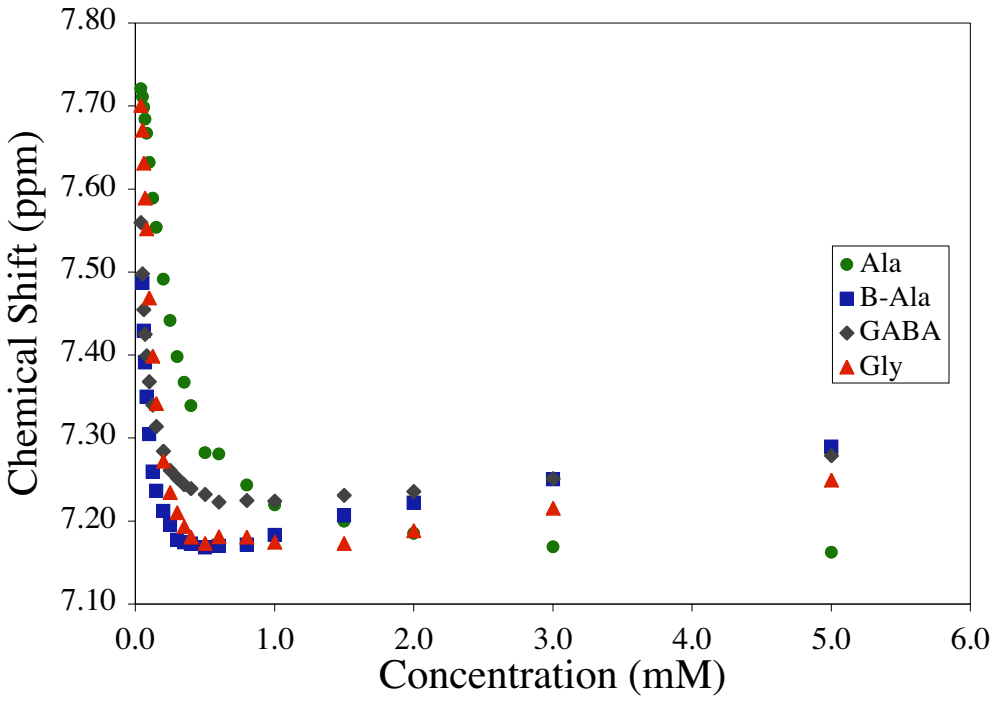


Figure 2-20. Dilution Studies of Interdigitated Homodimers in CD_3OD with 5% D_2O (Ala = dialaninodicarboxycalix[4]arene **104**; B-Ala = di-β-alaninodicarboxycalix[4]arene **105**; GABA = di-γ-aminobutyric acid dicarboxycalix[4]arene **106**; Gly = dicarboxydiglycinocalix[4]arene **103**)

2.4 Water-Soluble Calix[4]arene Derivatives

In order for calix[4]arene capsules to be used for drug delivery and other biological applications, the capsules must be water-soluble. Although the propoxycalix[4]arene derivatives contain ionic groups on their upper rims, the capsules are not water-soluble. This is due to the shielding of the charges upon assembly leaving only the hydrophobic propyl groups on the lower rim exposed to the polar solvent. Calix[4]arene derivatives are being synthesized with hydroxy ethyl groups instead of the propyl groups on the lower rim and. The hydroxyethoxycalix[4]arene derivatives will

dimerize into homo- or heterodimers with the lower rim alcohols exposed to the polar solvent (Figure 2-21). This will increase the water-solubility of the capsule.

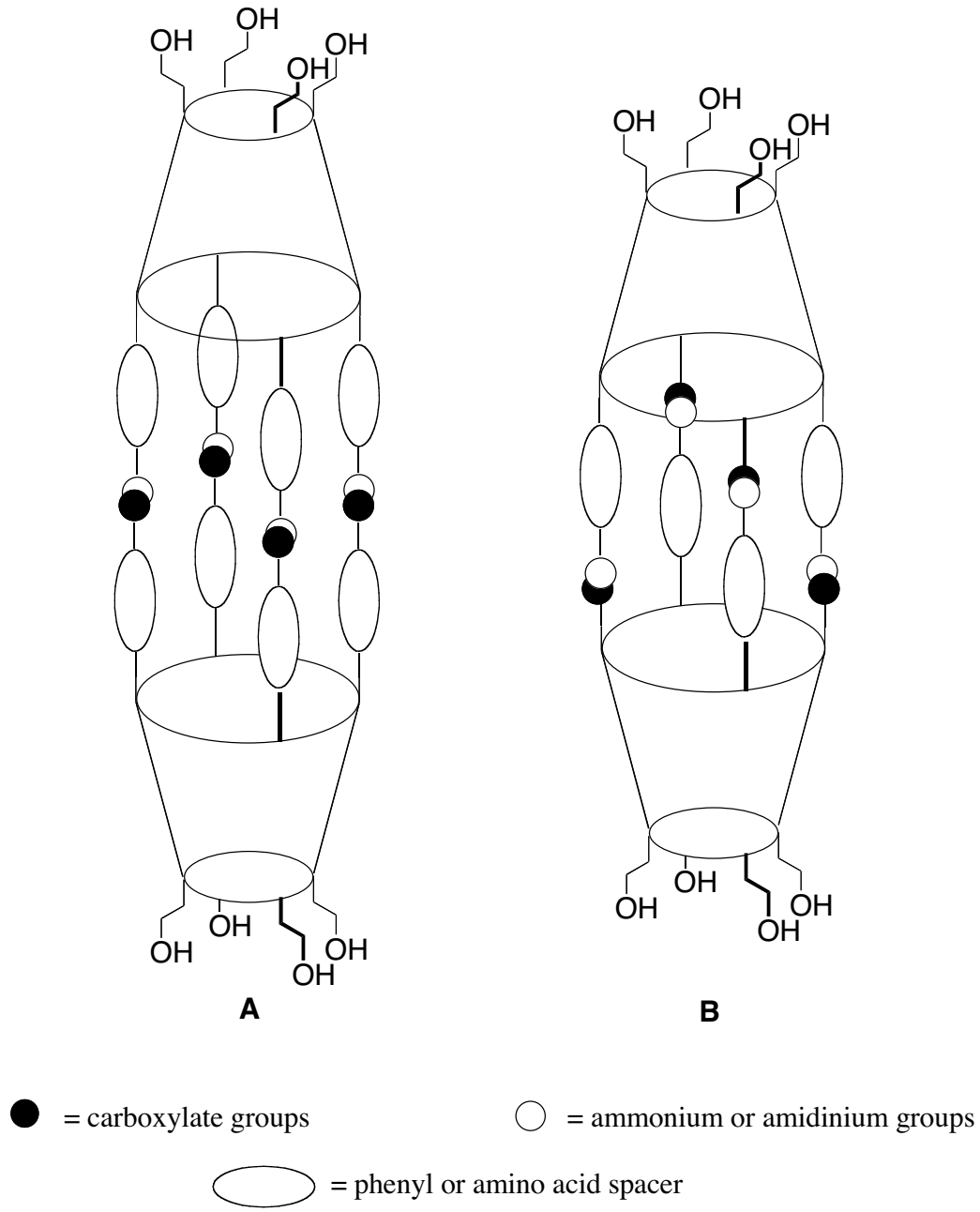


Figure 2-21. Water-Soluble Calix[4]arene Dimer Structures

2.4.1 Towards the Synthesis of Water-Soluble Calix[4]arene Heterodimer Derivatives

The synthesis of water-soluble calix[4]arene heterodimers (**A**, Figure 2-21) has been attempted through several different synthetic schemes. The first target was anilinohydroxyethoxycalix[4]arene (**118**) which would then be used to synthesize several tetrasubstituted hydroxyethoxycalix[4]arene derivatives **119a-d** and **120a-d** (Figure 2-22). The synthesis of *t*-butylethylacetoxycalix[4]arene (**125**, Scheme 2-9) was the first step in the route to **118**. After several different attempts (Table 2-1) at synthesizing the ester unsuccessfully from *t*-butylcalix[4]arene (**92**, Scheme 2-9), a new target was chosen.[39] In the unsuccessful attempts, several different products were formed with various degrees of alkylation and in other non-cone conformations (Figure 1-11).

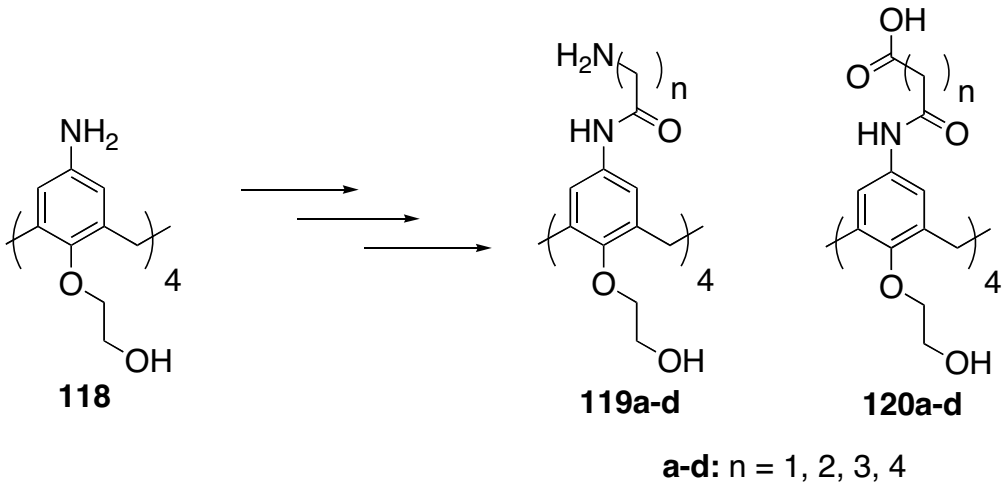
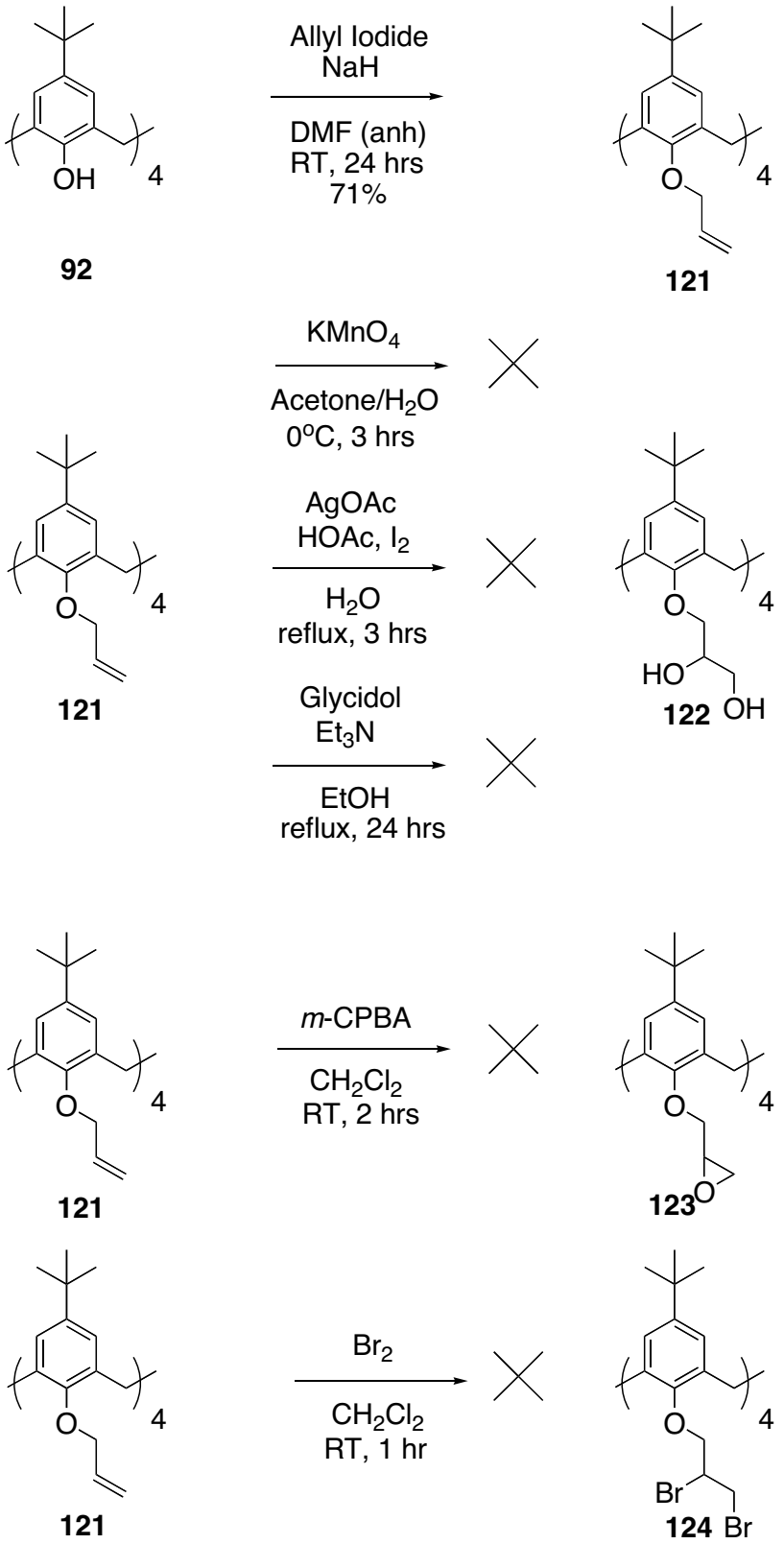


Figure 2-22. Water-Soluble Calix[4]arene Heterodimer Derivatives

Table 2-1. Attempted Synthesis of *t*-Butylethylacetoxycalix[4]arene (**125**, Scheme 2-9) from *t*-Butylcalix[4]arene **92**

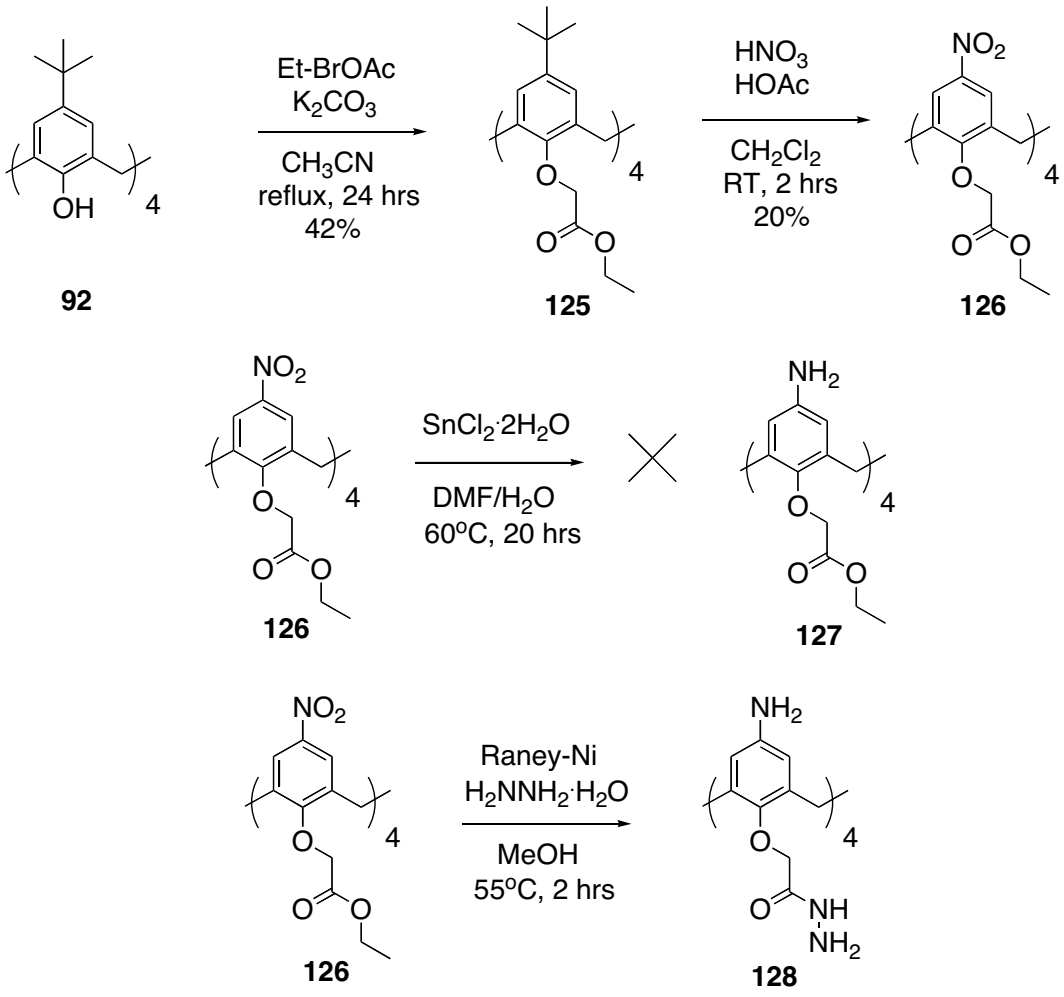
Reagent	Base	Solvent	Temperature	Time
Ethyl Bromoacetate	NaH	DMF (anh)	R.T.	24 hrs
Ethyl Bromoacetate	K_2CO_3	Acetone	Reflux	24 hrs
Ethyl Bromoacetate	K_2CO_3	DMF (anh)	70 °C	24 hrs
Ethyl Bromoacetate	Cs_2CO_3	DMF (anh)	70 °C	24 hrs
Ethyl Iodoacetate	NaH	DMF (anh)	R.T.	24 hrs
Ethyl Iodoacetate	K_2CO_3	Acetone	Reflux	24 hrs
Ethyl Iodoacetate	NaH	THF (anh)	67 °C	24 hrs

The new target was *t*-butyl(1,2-dihydroxypropoxy)calix[4]arene (**122**) (Scheme 2-8). *t*-Butylcalix[4]arene (**92**) was reacted with allyl iodide and sodium hydride in anhydrous dimethyl formamide to form *t*-butylallylcalix[4]arene (**121**). Oxidation of **121** with potassium permangenate,[40, 41] was attempted but no reaction occured. Oxidation was also attempted with silver acetate/iodine/acetic acid,[42] and *m*-chloroperoxybenzoic acid (*m*-CPBA). While the double bond did react, mixtures containing several different products were formed. Bromination of the double bond was also attempted but yielded a mixture of unseparable products. *t*-Butylallylcalix[4]arene (**121**) was refluxed with glycidol and triethylamine in ethanol but no reaction occured.[43]



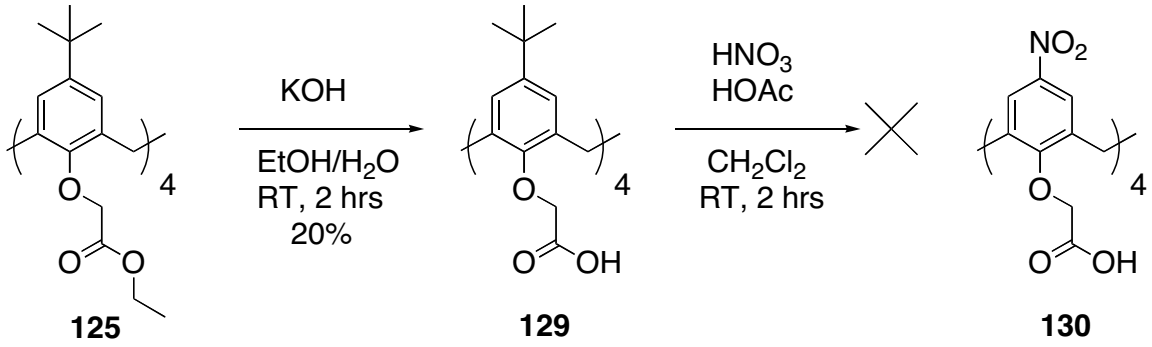
Scheme 2-8. Attempted Synthesis of *t*-Butyl(1,2-dihydroxypropoxy)calix[4]arene **122**

Do to the lack of success using *t*-butylallylcalix[4]arene (**121**), our focus shifted back to the synthesis of the first target, anilinohydroxyethoxycalix[4]arene (**118**, Figure 2-22). Ethyl bromoacetate and potassium carbonate in refluxing acetonitrile were found to convert *t*-butylcalix[4]arene (**92**) into the desired *t*-butylethylacetoxycalix[4]arene (**125**) (Scheme 2-9). The ester derivative **125** was then nitrated with nitric acid and acetic acid in methylene chloride. The reduction of the nitrohydroxyethoxycalix[4]arene (**126**) with tin chloride dihydrate[44] in dimethyl formamide and water was unsuccessful, no reaction occured. When heated in methanol with Raney nickel and hydrazine,[27] the nitro group of **126** was reduced, but the hydrazine reacted with the ester also to form the corresponding hydrazide.



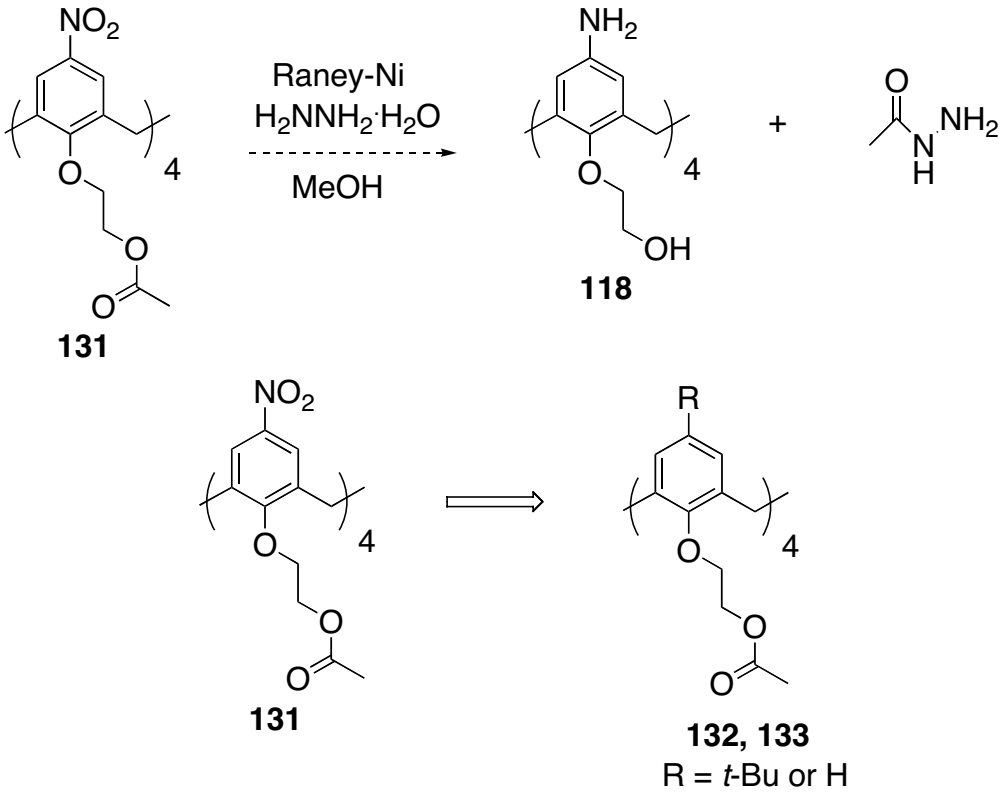
Scheme 2-9. Towards the Synthesis of Anilinoethylacetoxycalix[4]arene **118**

In order to avoid the reaction of hydrazine with the ester group, **125** was hydrolyzed with potassium hydroxide in refluxing ethanol to yield *t*-butylcalix[4]arene acetic acid (**129**) (Scheme 2-10). No reaction proceeded from the attempted nitration of **129** using nitric acid and acetic acid in methylene chloride. Nitration of *t*-butylhydroxyethoxycalix[4]arene under the same conditions was attempted by Suazette Reid with no success.



Scheme 2-10. Towards the Synthesis of Anilinohydroxyethoxycalix[4]arene **118**

By changing the orientation of the oxygen and carbonyl in the ester derivative, the reaction of hydrazine with the ester would produce the desired product anilinohydroxyethoxycalix[4]arene (**118**) (Scheme 2-11). Unfortunately, none of the reactions of *t*-butylcalix[4]arene (**92**) or calix[4]arene (**93**, Scheme 2-1) with bromoethylacetate and potassium carbonate in refluxing acetonitrile were successful (Table 2-2).



Scheme 2-11. Towards the Synthesis of Anilinohydroxyethoxycali[4]arene **118**

Table 2-2. Attempted Synthesis of calix[4]arene-ethoxyacetate derivatives **132** or **133** from *t*-Butylcalix[4]arene **92** or calix[4]arene **93**

S.M.	Reagent	Base	Solvent	Temperature	Time
92	Bromoethylacetate	K_2CO_3	CH_3CN	Reflux	24 hrs
93	Bromoethylacetate	K_2CO_3	CH_3CN	Reflux	24 hrs
93	Bromoethylacetate	K_2CO_3, KI	CH_3CN	Reflux	24 hrs
93	Bromoethylacetate	K_2CO_3	none	80 °C	24 hrs
93	Bromoethylacetate	K_2CO_3, KI	none	80 °C	24 hrs

S.M. = starting material

2.4.2 Towards the Synthesis of Water-Soluble Calix[4]arene Homodimer Derivatives

The synthesis of water-soluble interdigitated calix[4]arene homodimers (**B**, Figure 2-21) is underway. The main target is dianilinodicarboxyhydroxyethoxycalix[4]arene (**134**), which could then be used to synthesize ionic hydroxyethoxycalix[4]arene derivatives **135a-d** disubstituted with amino acids and carboxylic acids on the upper rim (Figure 2-23). Using the knowledge gained from attempting to synthesize water-soluble heterodimers, hydroxyethoxycalix[4]arene (**136**) was the first target in the route to **134**. Several attempts at synthesizing hydroxyethoxycalix[4]arene directly from calix[4]arene (**93**) were unsuccessful (Scheme 2-12). Bromopropanol was not reactive enough to successfully react with **93**. Ethylacetoxycalix[4]arene (**137**) was synthesized by refluxing **93** with ethyl bromoacetate and potassium carbonate in acetonitrile. The ester was then reduced with lithium aluminum hydride in tetrahydrofuran to form hydroxyethoxycalix[4]arene (**136**).[45] All attempts at nitrating **136** with nitric acid and acetic acid in methylene chloride led to a mixture containing several unseparable products.

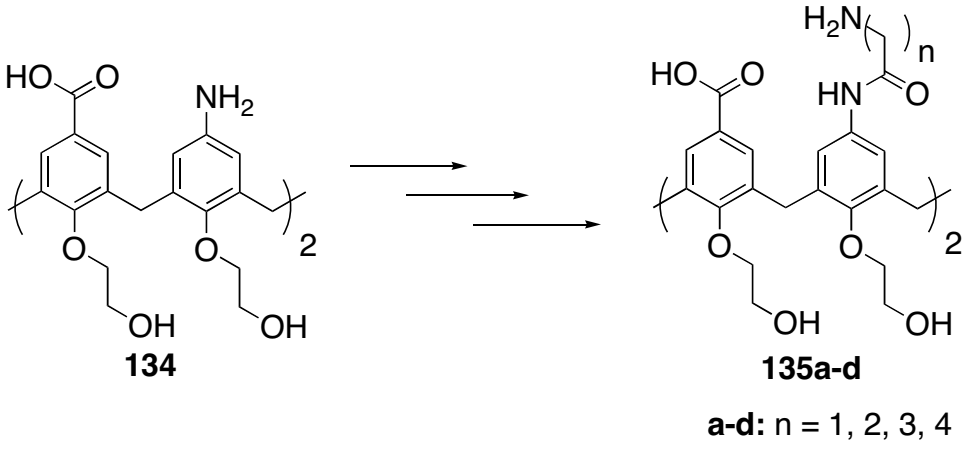
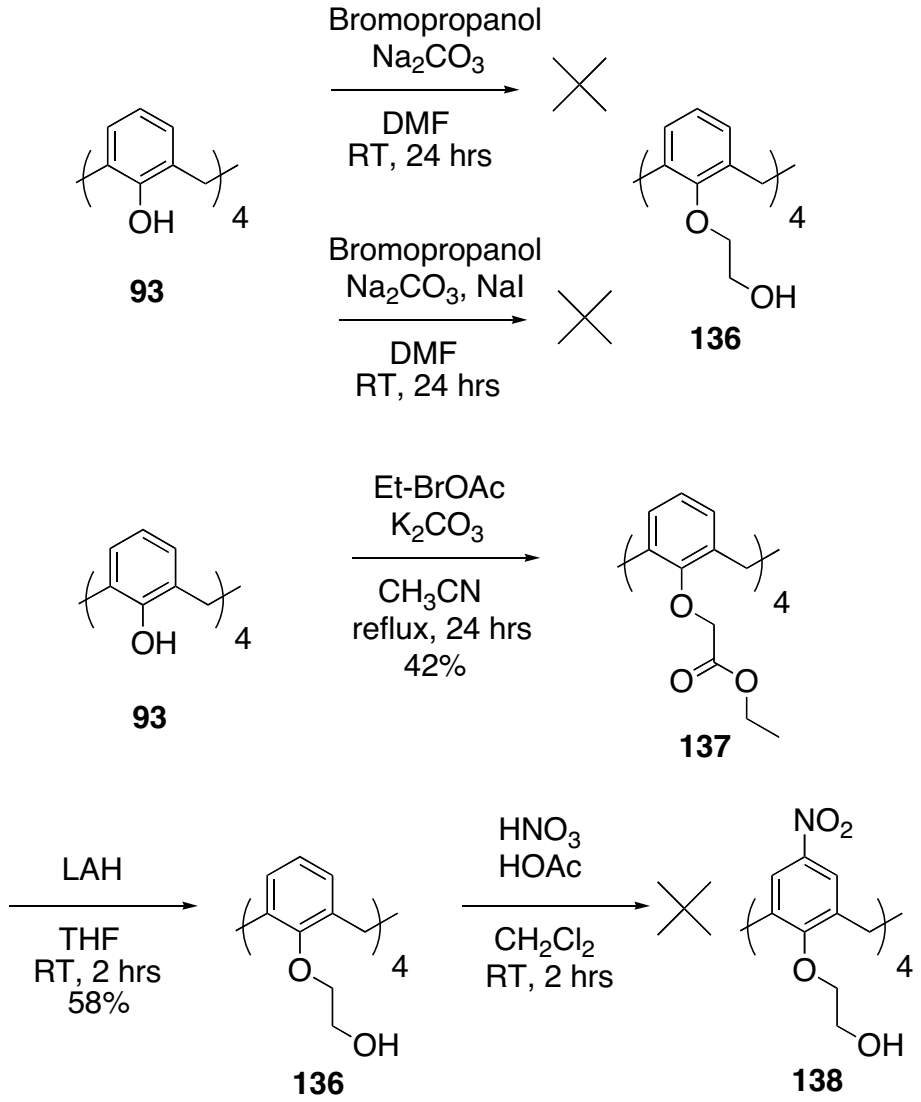
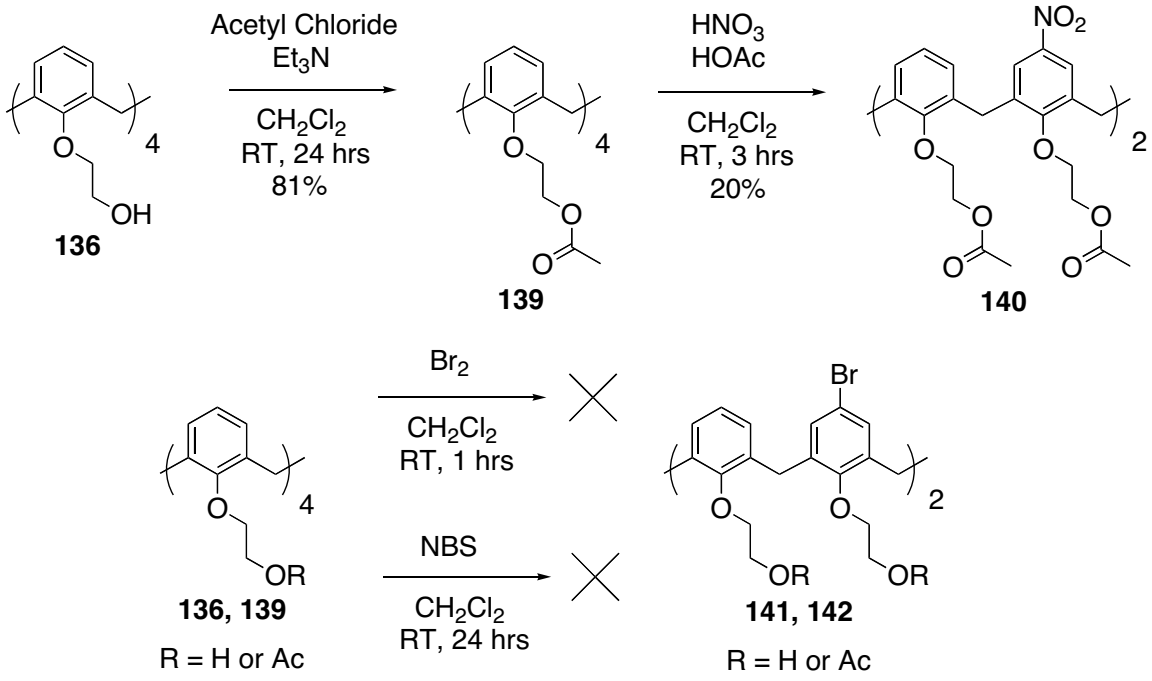


Figure 2-23. Water-Soluble Calix[4]arene Homodimer Derivatives



Scheme 2-12. Towards the Synthesis of Dianilinodicarboxyhydroxyethoxycalix[4]arene **134**

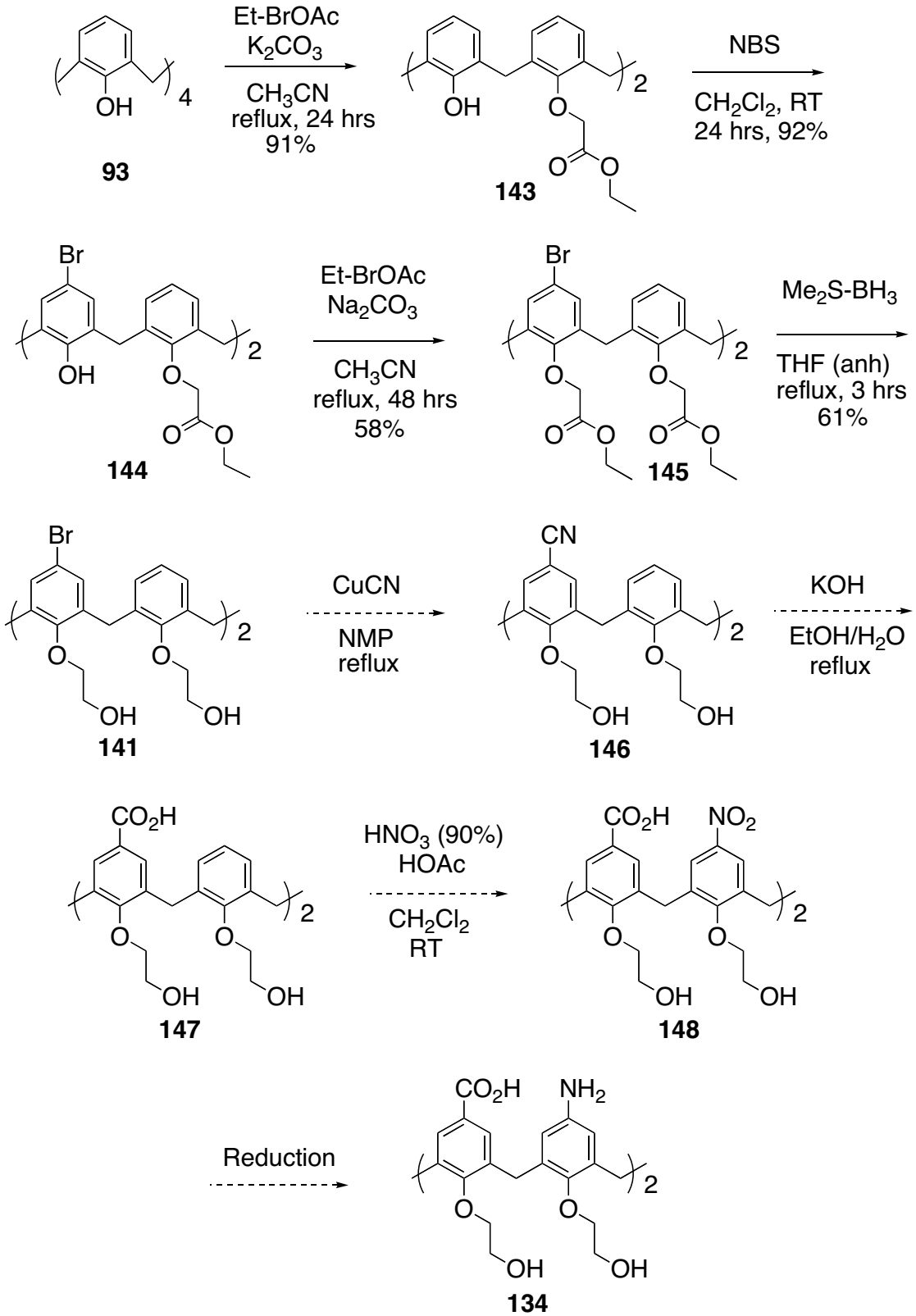
Calix[4]arene-ethoxyacetate (**139**) was synthesized by treating hydroxyethoxycalix[4]arene (**136**) with acetyl chloride and triethylamine in methylene chloride (Scheme 2-13). The ester derivative **139** was nitrated using nitric acid and acetic acid in methylene chloride to give dinitrocalix[4]arene-ethoxy acetate (**140**).[46] Although the nitration did work, it required difficult purification resulting in low yields. Attempts at dibromination of **136** and **139** with bromine or *N*-bromosuccinamide in methylene chloride only led to a mixture of brominated products.



Scheme 2-13. Towards the Synthesis of Dianilinodicarboxyhydroxyethoxycalix[4]arene **134**

Due to the inability to disubstitute hydroxyethoxycalix[4]arene (**136**), a new scheme, similar to the one for synthesizing dicarboxydiglycinocalix[4]arene (**103**, Scheme 2-5), was adopted (Scheme 2-14). Calix[4]arene (**93**) was treated with 2.2

equivalents of ethyl bromoacetate and 1.1 equivalents of potassium carbonate in refluxing acetonitrile to yield diethylacetoxycalix[4]arene (**143**).[47] As seen in Scheme 2-5, the dibromo derivative **143** is formed exclusively due to the increased reactivity of the unsubstituted phenol rings over the alkylated phenol rings. The disubsituted derivative **143** was dibrominated with *N*-bromosuccinamide in methylene chloride. Dibromodiethylacetoxycalix[4]arene (**144**) was refluxed with 10 equivalents of ethyl bromoacetate and 10 equivalents of sodium carbonate in acetonitrile to form dibromoethylacetoxycalix[4]arene (**145**).[47] The esters were reduced with methylsulfide-borane complex in THF to form dibromohydroxyethoxycalix[4]arene (**141**).[48] All attempts at converting the bromides into nitriles have been unsuccessful thus far. After the nitrile derivative is synthesized, it will be hydrolyzed with potassium hydroxide to the acid derivative **147**. The acid derivative **147** will be nitrated and the nitro groups reduced to form the desired product dianilinodicarboxyhydroxyethoxycalix[4]arene (**134**).

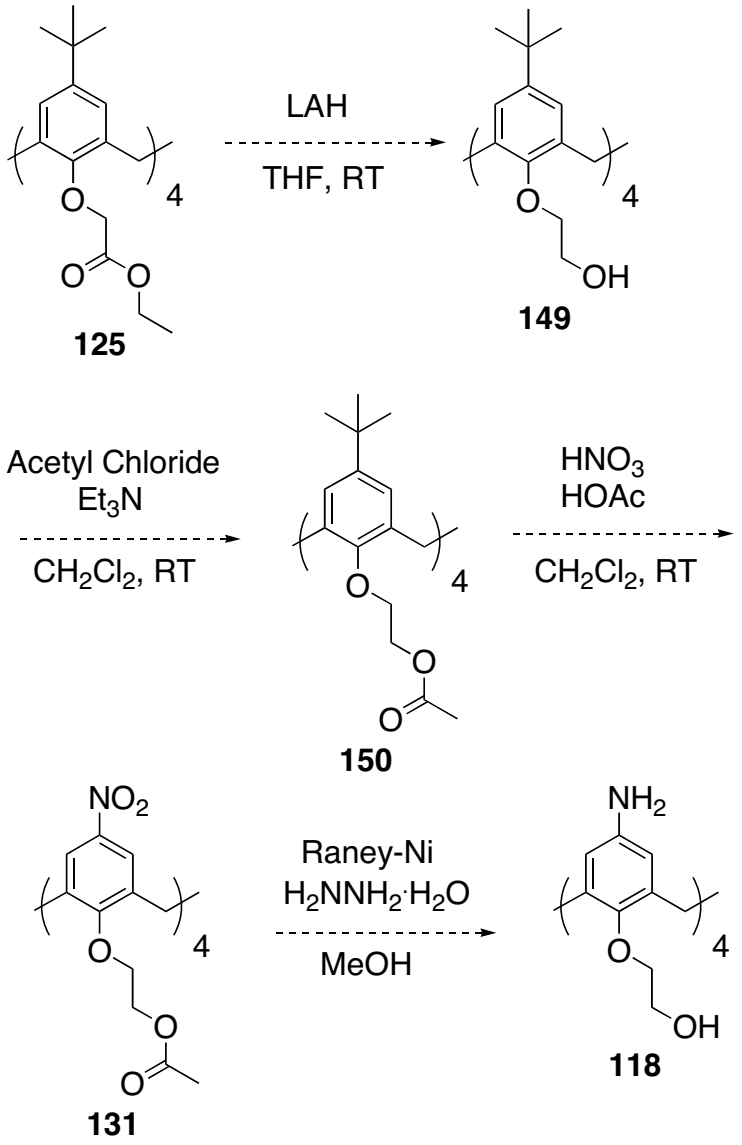


Scheme 2-14. Towards the Synthesis of Dianilinodicarboxyhydroxyethoxycalix[4]arene **134**

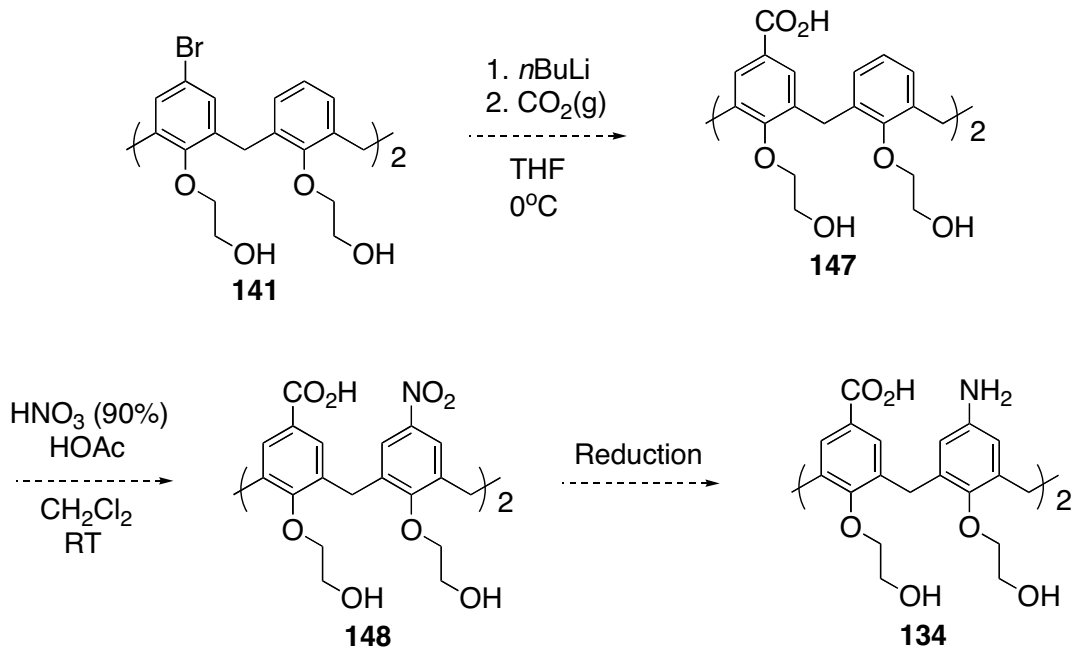
2.4.3 Water-Soluble Calix[4]arene Derivative Results

The synthesis of water-soluble calix[4]arene heterodimers is well underway. Several different routes to anilinohydroxyethoxycalix[4]arene (**118**) were attempted with some success. Nitroethylacetoxycalix[4]arene (**126**) was synthesized but the reduction of the nitro groups to form the aniline derivative **118** resulted in the formation of the undesired byproduct **128** (Scheme 2-9). A new proposed route to the synthesis of anilinohydroxyethoxycalix[4]arene (**118**), using some of the knowledge gained from the homodimer derivative synthesis, is seen in Scheme 2-15. Reduction of *t*-Butylethylacetoxycalix[4]arene (**125**) with lithium aluminum hydride will form the alcohol derivative **149**, which will be acylated with acetyl chloride to form *t*-butylcalix[4]arene-ethoxyacetate (**150**). Acetate **150** will be nitrated and then reduced with Raney nickel to form the desired product anilinohydroxyethoxycalix[4]arene (**118**).

The synthesis of water-soluble calix[4]arene homodimers is also underway. Several different routes to dianilinodicarboxyhydroxyethoxycalix[4]arene (**134**) were attempted with some success. Dibromohydroxyethoxycalix[4]arene (**141**) has been synthesized and more work needs to be done in order to convert the bromides into nitriles (Scheme 2-14). If it is not possible to complete this transformation, the bromides may be directly converted into carboxylic acids with lithium aluminum hydride and carbon dioxide (Scheme 2-16).[25] The acid derivative **147** could be nitrated and the nitro groups reduced to form the desired product dianilinodicarboxyhydroxyethoxycalix[4]arene (**134**).



Scheme 2-15. New Route to the Synthesis of Anilinohydroxyethoxycalix[4]arene **118**



Scheme 2-16. New Route to the Synthesis of Dianilinodicarboxyhydroxyethoxycalix[4]arene **134**

2.5 Calix[4]arene Dimer Conclusions

The ability of calix[4]arene derivatives to self-assemble in polar solvents has been demonstrated. *C*-linked-alaninocalix[4]arene (**84**) dimerizes with *N*-linked-alaninocalix[4]arene (**85**), carboxycalix[4]arene (**87**), and carboxyphenylcalix[4]arene (**88**) in the DMSO-d_6/5% phosphate buffer at pH 6.5 as shown in Figure 2-13. The monomers with the largest pK_a difference formed the strongest dimer **84:85** (K_a = 5040 M^{-1}) followed by **84:88** (K_a = 4410 M^{-1}) and **84:87** (K_a = 1200 M^{-1}). It is interesting to note that addition of the phenyl spacers to the calix[4]arene scaffold increases the size of the capsule with little effect on its ability to dimerize.

All of the interdigitated calix[4]arene derivatives have similar association curves upon dilution. Dialaninodicarboxycalix[4]arene (**104**, K_a = 700 M^{-1}) formed the strongest dimer in CD_3OD with 5% phosphate buffer (pH 6.5) followed by diglycinodicarboxy-

calix[4]arene (**103**, K_a = 497 M^{-1}), di-β-alaninodicarboxycalix[4]arene (**105**, K_a = 430 M^{-1}), and last di-GABA-dicarboxycalix[4]arene (**106**, K_a = 180 M^{-1}) (Figure 2-19). The chain length of the amino acid does have an affect on the binding affinity in the CD_4OD/buffer solution. The longer chain lengths cause a decrease in the association strength of the dimer. The incresed flexibility of the longer chains might weaken the association strength of the dimer. In CD_3OD with 5% D_2O, the β-alanine derivative **105** forms the strongest complex followed closely by the GABA derivative **106**, glycine derivative **103**, and the alanine derivative **104** (Figure 2-20). While the derivatives do associate into complexes in 95% deuterated methanol with 5% D_2O, they do not form dimers. The true nature of the complexes is still not fully understood. The chain length of the amino acid does not seem to have an affect in the association of the derivatives in the CD_3OD/D_2O solution suggested that the derivatives are associating in a different way than the dimers formed in the CD_3OD/phosphate buffer solution.

The synthesis of water-soluble calix[4]arene heterodimers is well underway, several different routes to anilinohydroxyethoxycalix[4]arene (**118**) have been attempted. Nitroethylacetoxycalix[4]arene (**126**) was synthesized but the reaction to reduce the nitro groups to form the aniline derivative **118** ended up reacting with the ester also (Scheme 2-9). A new route to the synthesis of anilinohydroxyethoxycalix[4]arene (**118**) is shown in Scheme 2-15. The synthesis of water-soluble homodimers is also underway, several different routes to dianilinodicarboxyhydroxyethoxycalix[4]arene (**134**) have been attempted. Dibromohydroxyethoxycalix[4]arene (**141**) has been synthesized and more work needs to be done in order to synthesize dicarboxyhydroxyethoxycalix[4]arene (**147**) (Schemes 2-14 and 2-15).

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CHAPTER 3

EXPERIMENTAL AND SPECTRAL DATA

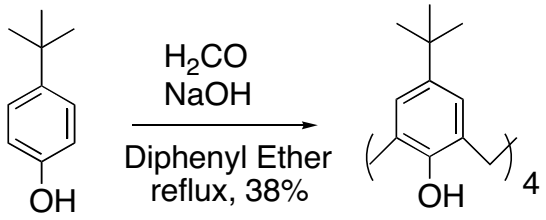
3.1 General Conditions

Concentration of solutions was accomplished using a Labconco rotary evaporator with a Neuberger Laboport vacuum pump. This was followed by removal of residual solvent under high vacuum. Unless otherwise stated, reagents and solvents were used as received from the manufacturer without further purification. Anhydrous tetrahydrofuran was distilled from sodium-benzophenone ketyl under positive pressure of argon.

Reactions were monitored by thin layer chromatography using 0.25 mm silica gel 60 plates impregnated with a 254 nm florescent indicator. Plates were visualized by UV light and/or using anisaldehyde, iodine, or potassium permanganate as staining agents. Column chromatography was performed using silica gel 60, 230–400 mesh as a stationary phase.

Melting points were recorded on a MelTemp II apparatus and are uncorrected. NMR spectra were recorded on a Varian-Gemini-400 magnetic resonance spectrometer. Proton NMR spectra are recorded in parts per million (ppm) relative to the peak of $CDCl_3$ (7.24 ppm), DMSO-d_6 (2.49 ppm), or CD_3OD (3.30 ppm). Carbon-13 spectra were recorded relative to the central peak of the chloroform-d_1 triplet (77.0 ppm), the DMSO-d_6 septet (39.7 ppm), or the methanol-d_4 septet (49.0 ppm), and were recorded with complete hetero-decoupling. High-resolution mass spectra were recorded at the Georgia Institute of Technology mass spectrometry facility at Georgia Institute of Technology in Atlanta.

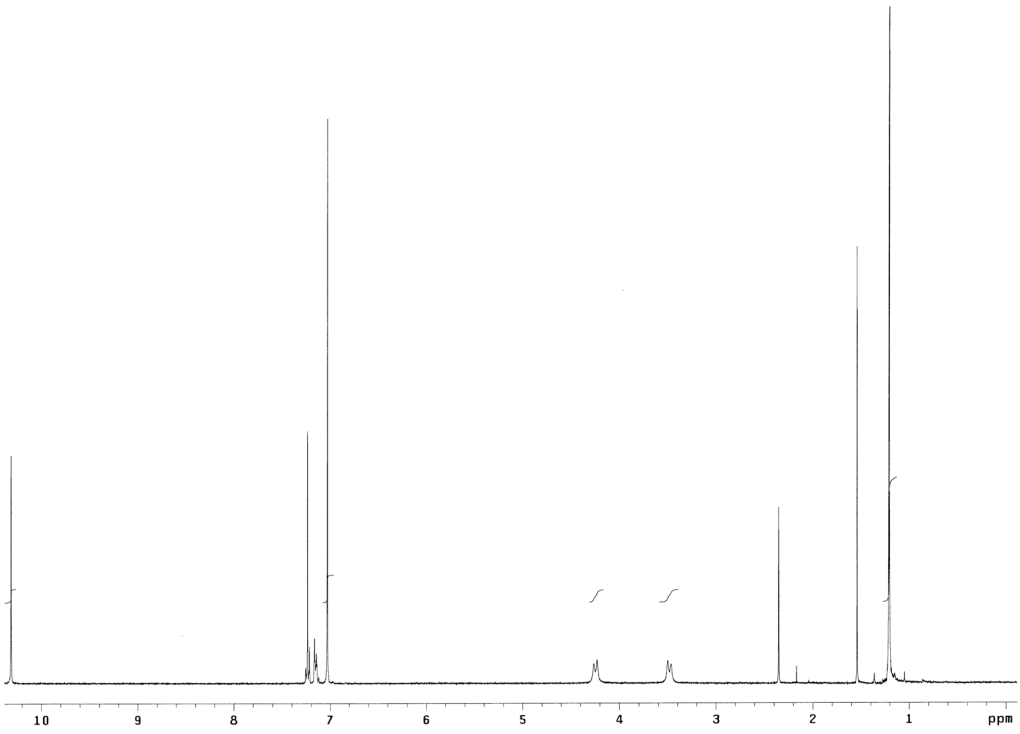
3.2 Experimental



91 **92**

Synthesis of *t*-Butylcalix[4]arene 92[1]

p-*t*-Butylphenol **91** (5 g, 1 eq) was added to a 37% formaldehyde (1.15 eq)/water solution in a three-neck round bottom flask. A 40% sodium hydroxide (0.036 eq)/water solution was added to the flask. The reaction was stirred for 15 minutes and then heated to 120^0C under a steady flow of nitrogen. After 3 hours, all of the reagents were dissolved forming a yellow, viscous solution. The reaction was cooled overnight and diphenyl ether (50 mL) was added. The reaction was heated back up to 120^0C and nitrogen was bubbled through the solution for 2 hours to remove water. The reaction was then refluxed for 3 hours and cooled overnight. Ethyl acetate was added and a white precipitate formed. The precipitate was removed by filtration and washed with ethyl acetate, acetic acid, deionized water, and acetone. The solid was then recrystallized from toluene. Gleaming white crystals were recovered (2.06 g, 38% yield). M.P. = 339-342 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 10.31 (s, 4 H), δ 7.03 (s, 8 H), δ 4.24 (d, 4 H, J = 13.2 Hz), δ 3.48 (d, 4 H, J = 12.8 Hz), δ 1.20 (s, 36 H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.5, 144.2, 127.5, 125.8, 32.7, 31.5; HRMS (FAB) Calcd. for $C_{44}H_{56}O_4$ (M^+): m/z = 671.4076 Found: m/z = 671.4089.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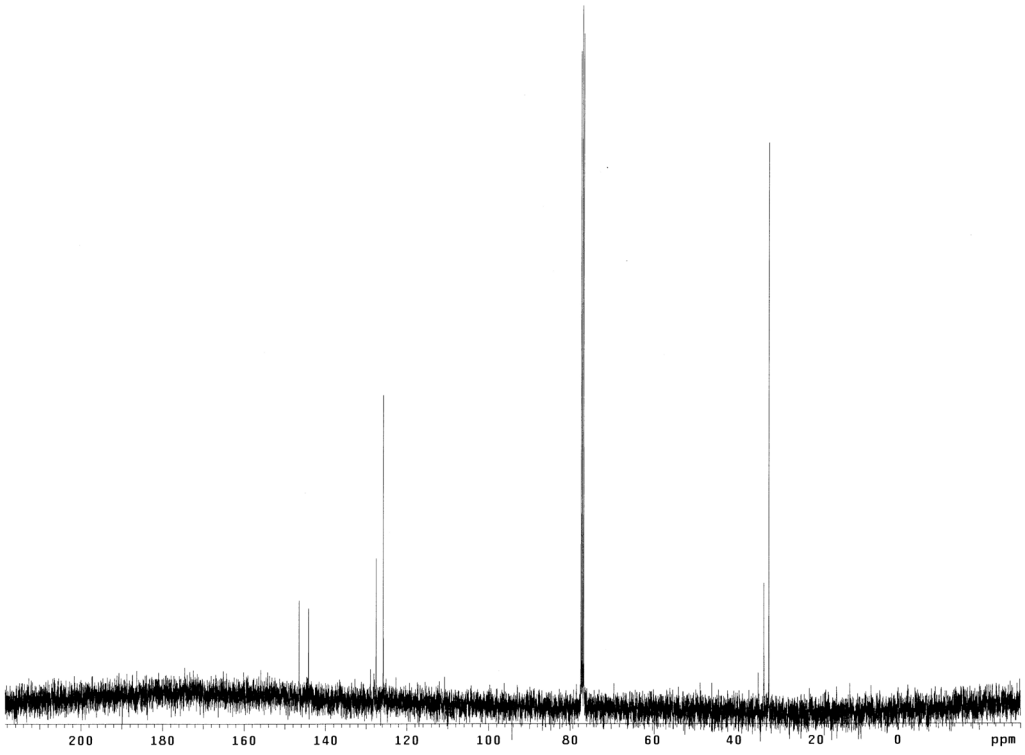
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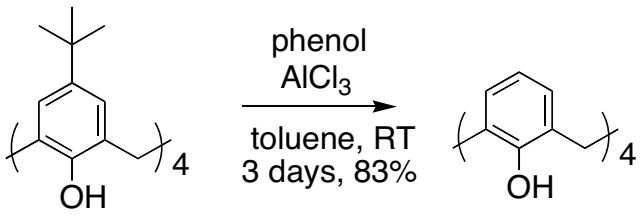
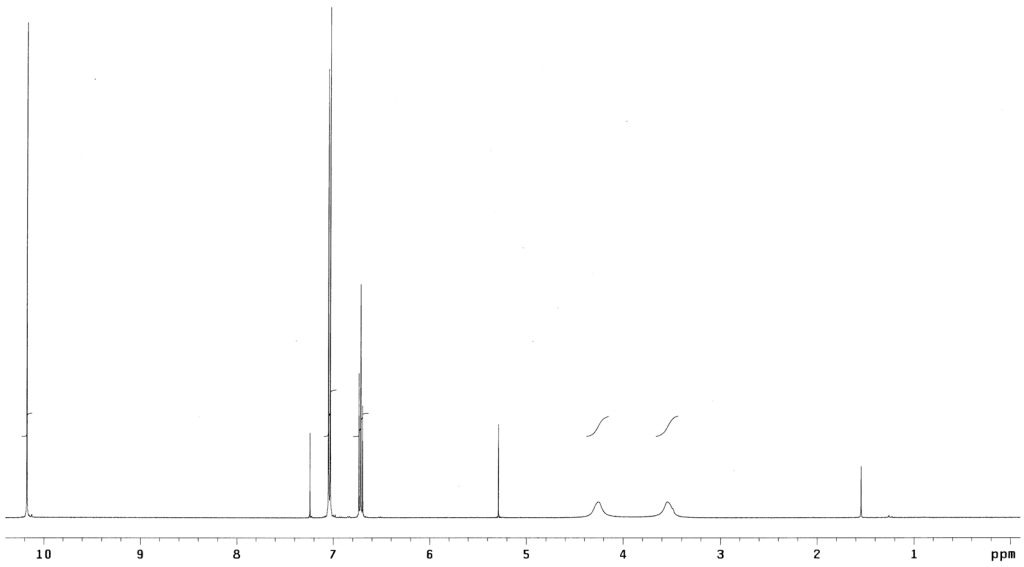


92 **93**

Synthesis of Calix[4]arene 93[1]

t-Butylcalix[4]arene **92** (50g, 1 eq) and aluminum trichloride (5.2 eq) were placed in a round bottom flask under nitrogen. Toluene (1 L) was added to the reaction and stirred. Phenol (4.8 eq) was added and the reaction was stirred for 3 days at room temperature. The reaction was then poured over dilute HCl (1.5 L, 0.2 M). The organic layer was washed with deionized water and brine. The organic layer was then dried over magnesium sulfate, filtered, and concentrated *in vacuo* until most of the toluene was gone. The product was precipitated out with methanol. The white solid was removed by filtration and washed with methanol (27 g, 83% yield). M.P. = 313.6-315.0 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 10.18 (s, 4 H), δ 7.04 (s, 4 H), δ 6.72 (t, 4 H, J = 7.5 Hz), δ 4.26 (br s, 4 H), δ 3.54 (br s, 4 H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 148.6, 128.8, 128.1, 122.1, 31.8; HRMS (FAB) Calcd. for $C_{28}H_{24}O_4$ (M^+): m/z = 425.1753 Found: m/z = 425.1768.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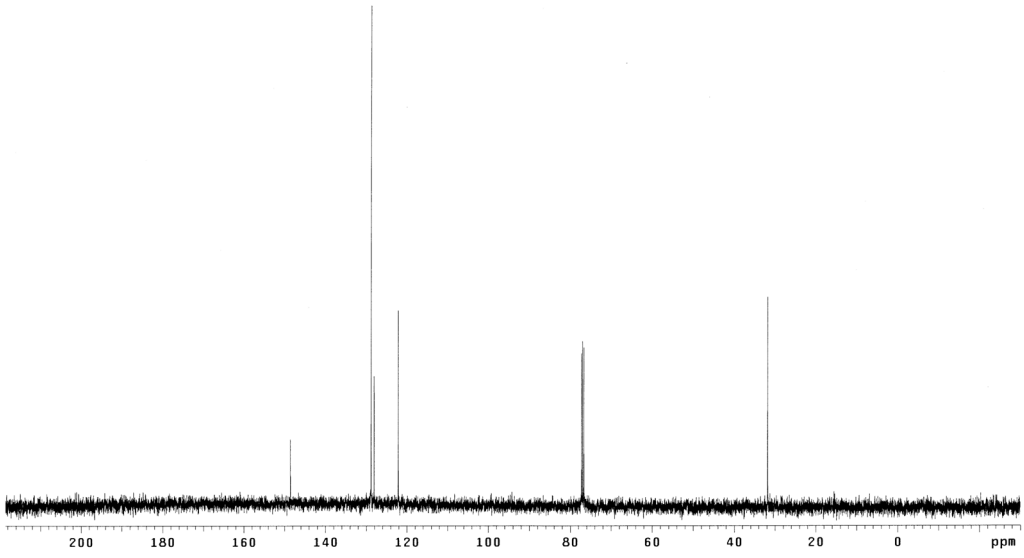
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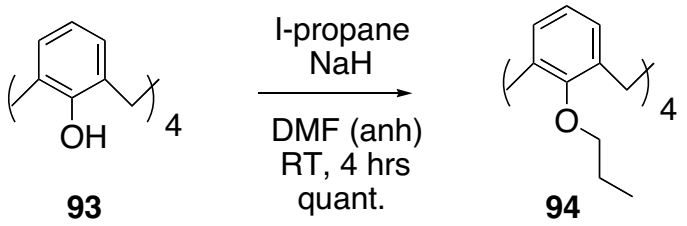
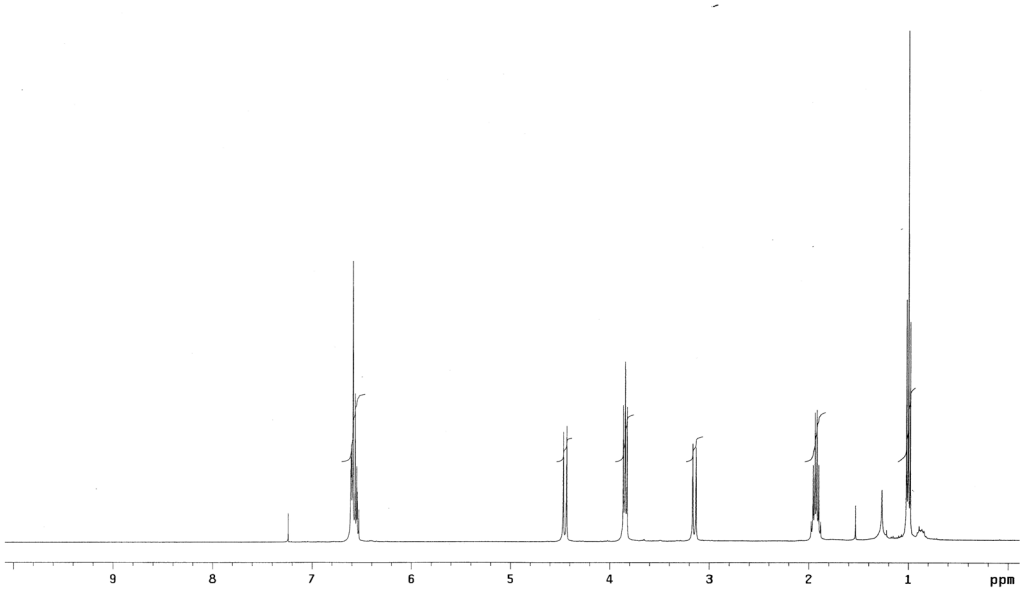


93 **94**

Synthesis of Tetrapropoxycalix[4]arene 94[2]

Calix[4]arene **93** (100 mg, 1 eq) was dissolved in anhydrous DMF (2.5 mL) in a round bottom flask under nitrogen. Sodium hydride (6 eq) was added and stirred for 30 minutes. Iodopropane (6 eq) was added and stirred at room temperature. The reaction was monitored by TLC (5:1, hexane:EtOAc). After 4 hours, the reaction looked complete. The reaction was extracted with methylene chloride and washed with saturated ammonium chloride, deionized water, and brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The product was recovered as an off-white solid (141 mg, >99%) and the structure was determined by NMR. M.P. = 199.3-200.0 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 6.61-6.55 (3, 12 H), δ 4.45 (d, 4 H, *J* = 13.2 Hz), δ 3.85 (t, 8 H, *J* = 7.5 Hz); δ 3.15 (d, 4 H, *J* = 13.6 Hz); δ 1.96-1.90 (m, 8 H); δ 1.00 (t, 12 H, *J* = 7.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.4, 135.0, 128.0, 121.7, 76.7, 31.1, 23.4, 10.5; HRMS (FAB) Calcd. for $C_{40}H_{48}O_4$ (M^{+Na}): *m/z* = 615.3450 Found: *m/z* = 6.15.3474.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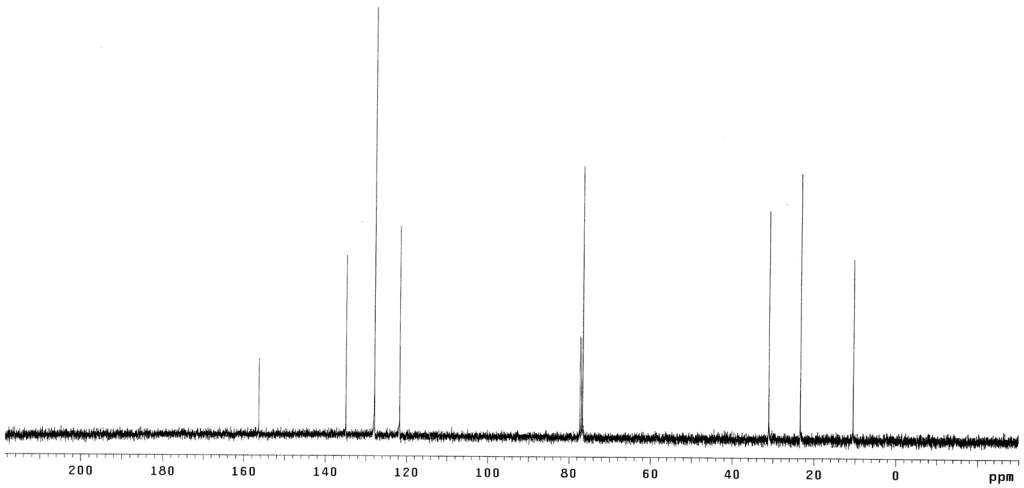
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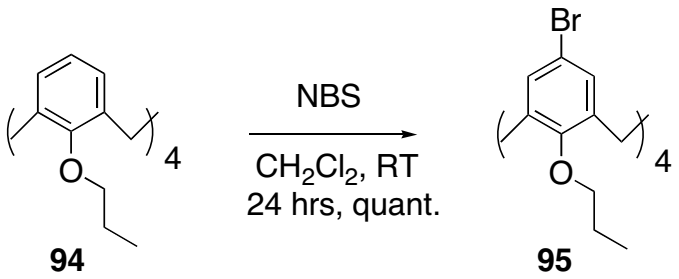
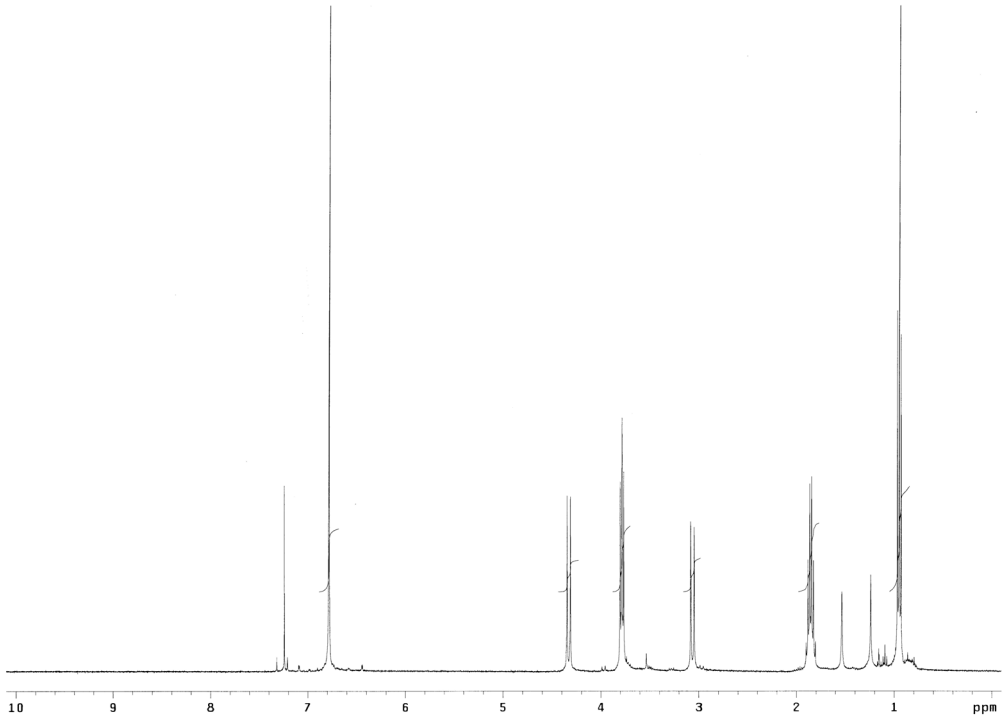


94 **95**

Synthesis of Tetrabromotetrapropoxycalix[4]arene 95

Tetrapropoxycalix[4]arene **94** (50 mg, 1 eq) was dissolved in methylene chloride (1 mL) in a round bottom flask under nitrogen. NBS (4.5 eq) was added and stirred at room temperature. The reaction was monitored by TLC (5:1, hexane:EtOAc). The NBS did not dissolve and no reaction was proceeding after 1 hour so methanol (0.5 mL) was added and stirred overnight. After 24 hours, the solution turned from clear to brown and the reaction looked complete. The reaction was washed with saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. A tan solid was recovered (78 mg, >99%). M.P. = 179 °C (dec.); ^{1}H NMR (400 MHz $CDCl_3$): δ 6.78 (s, 8 H), δ 4.33 (d, 4 H, *J* = 13.6 Hz), δ 3.78 (t. 8 H, *J* = 7.5 Hz), δ 3.06 (d, 4 H, *J* = 13.6 Hz), δ 1.85 (m, 8 H, *J* = 7.7 Hz), δ 0.95 (t, 12 H, *J* = 7.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 155.3, 136.3, 130.8, 115.0, 30.8, 23.2, 10.4; HRMS (FAB) Calcd. for $C_{40}H_{44}{}^{79}Br_4O_4$ (M^+): *m/z* = 903.99730 Found: *m/z* = 903.99104.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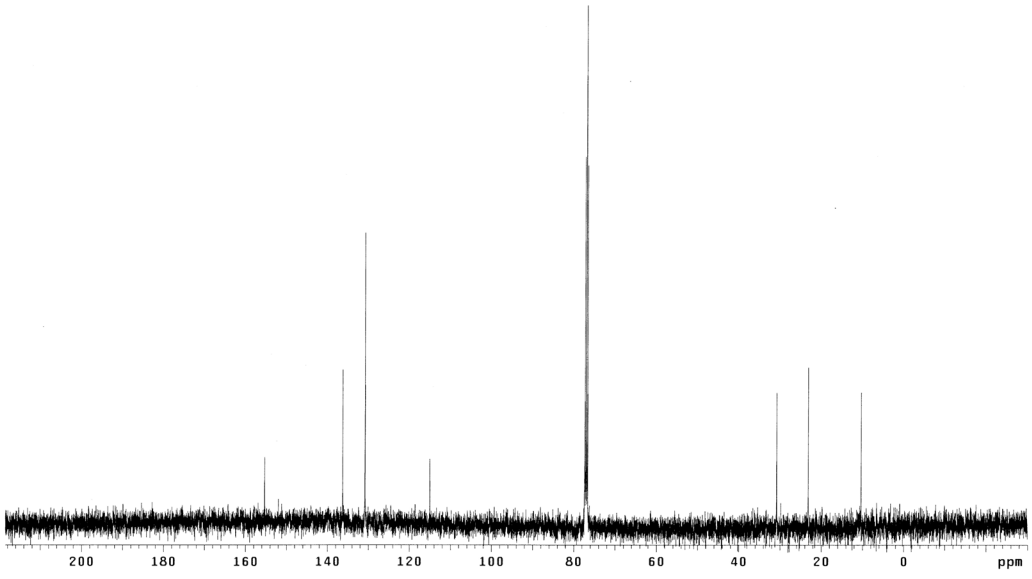
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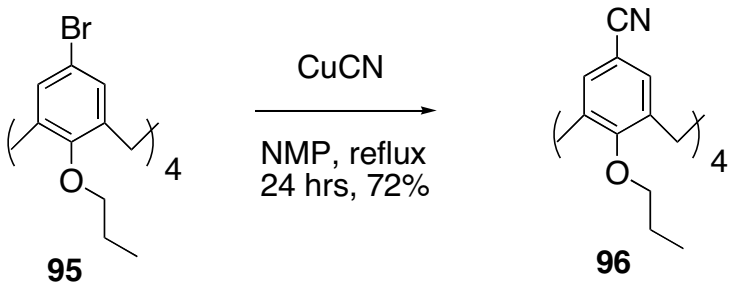
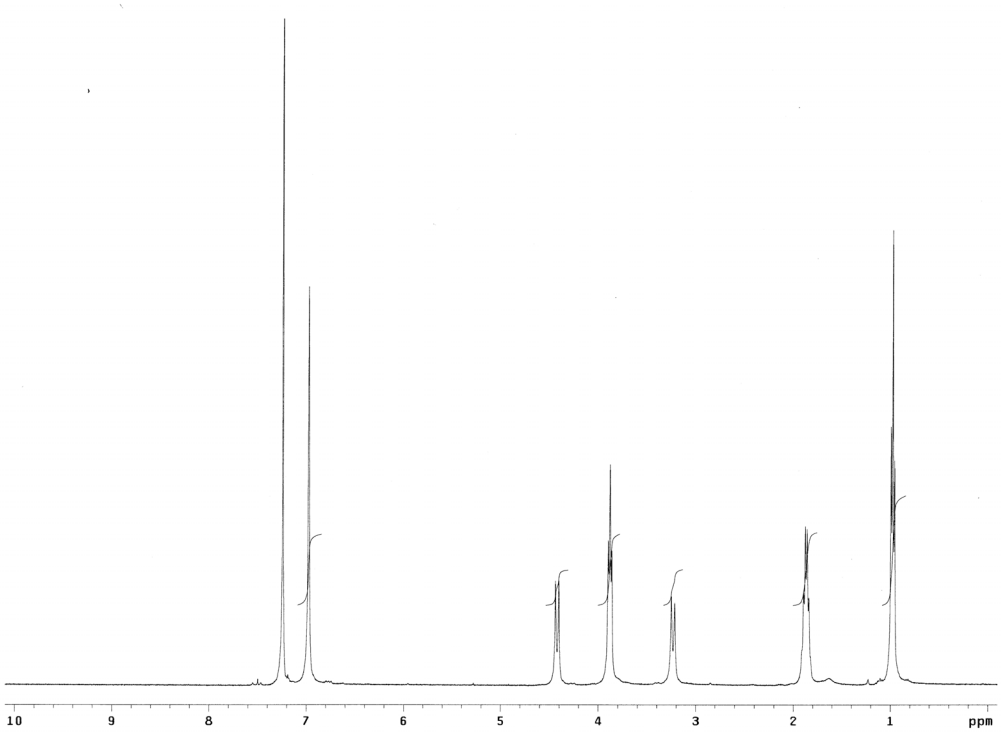


95 **96**

Synthesis of Tetranitrilotetrapropoxycalix[4]arene 96[3]

Tetrabromotetrapropoxycalix[4]arene **95** (50 mg, 1 eq) and copper cyanide (6 eq) were dissolved in *N*-methylpyrrolidinone (2 mL) in a round bottom flask under nitrogen. The reaction was refluxed overnight and turned from tan to a dark red/brown. The reaction was cooled to 100^0C and a solution of ferrous chloride hexahydrate (8 eq), HCl (0.25 mL) and deionized water (1.25 mL) was added and stirred for 1 hour. The reaction was then cooled to room temperature and filtered. The solid was washed with water and left on the filter to dry. The solid was then dissolved in methylene chloride and purified by column chromatography (CH_2Cl_2 then CH_2Cl_2:MeOH 99:1). The second fraction (1.6 g, 72%) was concentrated *in vacuo*. M.P. > 320 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 6.98 (s, 8 H), δ 4.42 (d, 4 H, *J* = 13.6 Hz), δ 3.88 (t. 8 H, *J* = 7.4 Hz), δ 3.23 (d, 4 H, *J* = 13.6 Hz), δ 1.87 (m, 8 H, *J* = 7.2 Hz), δ 0.98 (t, 12 H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 160.0, 135.6, 132.4, 118.2, 106.8, 77.5, 30.5, 23.2, 10.1; HRMS (FAB) Calcd. for $C_{44}H_{45}N_4O_4$ (M^{+1}): *m*/*z* = 693.34408 Found: *m*/*z* = 693.34638.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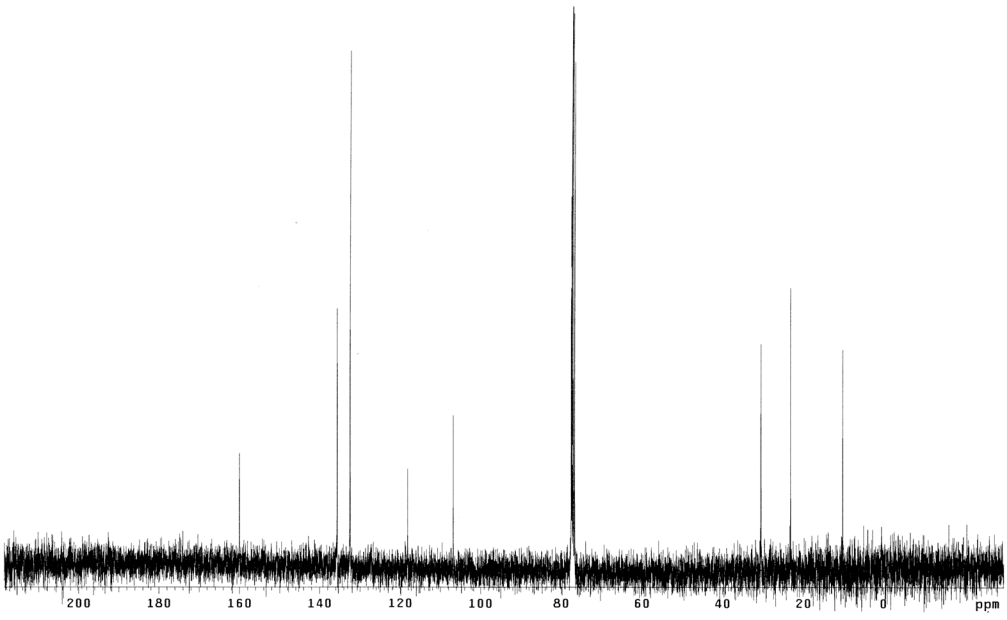
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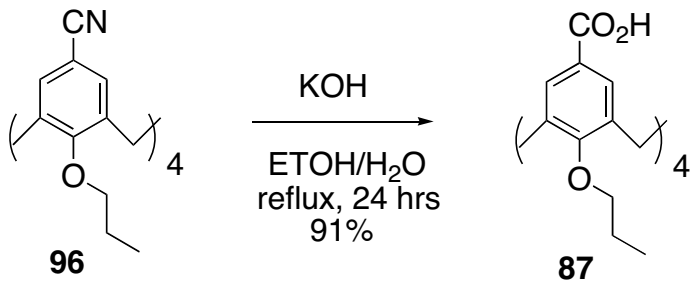
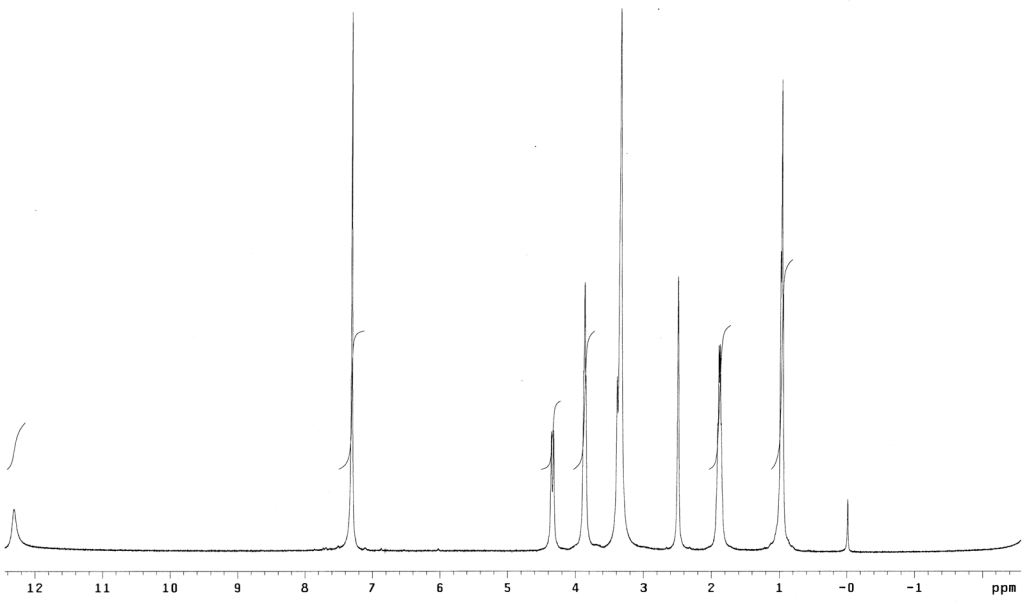


Synthesis of Tetracarboxytetrapropoxycalix[4]arene 87

Tetranitrilotetrapropoxycalix[4]arene **96** (500 mg, 1 eq) and ethanol (50 mL) were placed in a round bottom flask. Potassium hydroxide (40.5 g, 1000 eq) was dissolved in deionized water (50 mL) and added to the flask. The reaction was refluxed overnight. The reaction was acidified with concentrated hydrochloric acid and the product precipitated out. The precipitate (white solid, 503 mg, 91%) was removed by filtration and washed with deionized water and diethyl ether. M.P. > 320 °C; ^{1}H NMR (400 MHz DMSO-*d*6): δ 12.31 (s, 4 H), δ 7.31 (s, 8 H), δ 4.34 (d, 4 H, *J* = 12.8 Hz), δ 3.87 (t. 8 H, *J* = 6.4 Hz), δ 1.88 (m, 8 H, *J* = 7.0 Hz), δ 0.97 (t, 12 H, *J* = 6.8 Hz); ^{13}C NMR (400 MHz, DMSO-*d*6): δ 166.7, 159.8, 134.3, 129.6, 124.6, 76.7, 30.3, 23.1, 10.4; HRMS (FAB) Calcd. for $C_{44}H_{48}O_{12}$ (M^{+}): *m*/*z* = 768.31458 Found: *m*/*z* = 768.31730.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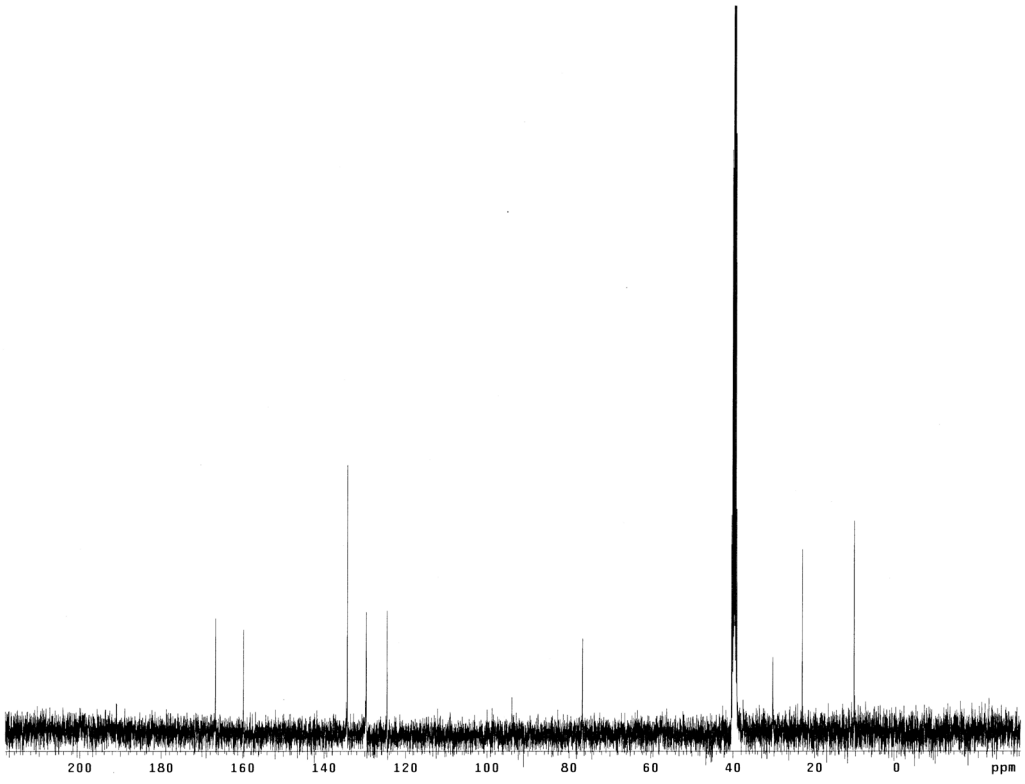
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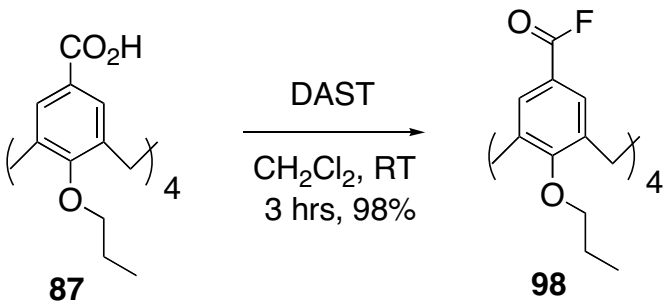
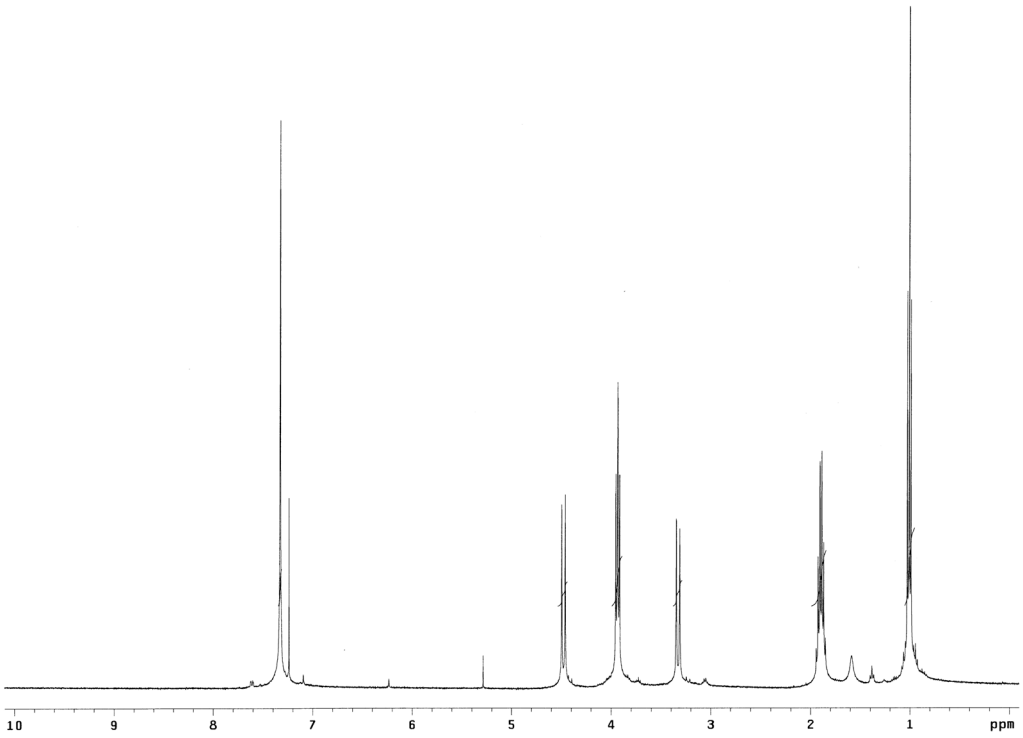


Synthesis of Tetracarboxyfluorotetrapropoxycalix[4]arene 97[4]

Tetracarboxytetrapropoxycalix[4]arene **87** (1.10 g, 1 e•) was dissolved in methylene chloride (15 mL) in a round bottom flask under nitrogen. Dimethylaminosulfur trifluoride (DAST, 2.30 mL, 12 eq) was added to the reaction. The reaction was stirred at room temperature and monitored by TLC (9:1, CH_2Cl_2: MeOH). After 3 hours, the reaction was quenched with ice-cold deionized water. The organic layer was separated and washed with more deionized water. The organic layer was then dried over magnesium sulfate and concentrated *in vacuo*. The crude product (tan solid, 1.1 g, 98%) was used without further purification. ^{1}H NMR (400 MHz $CDCl_3$): δ 7.33 (s, 8 H), δ 4.48 (d, 4 H, *J* = 14.0 Hz), δ 3.94 (t. 8 H, *J* = 7.4 Hz), δ 3.33 (d, 4 H, *J* = 14.0 Hz), δ 1.90 (m, 8 H, *J* = 7.6 Hz), δ 1.01 (t, 12 H, *J* = 7.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.3, 158.2, 154.8, 135.4, 131.9, 119.4, 118.8, 77.4, 30.9, 23.4, 10.3; HRMS (EI) Calcd. for $C_{44}H_{44}F_4O_8$ (M^+): *m*/*z* = 776.29723 Found: *m*/*z* = 776.29433.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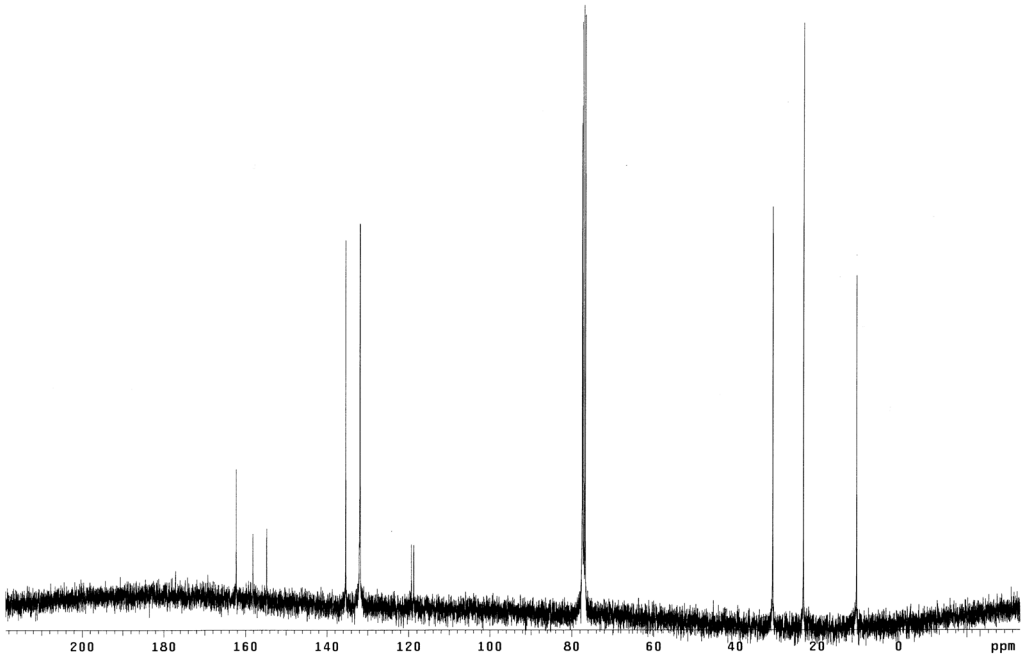
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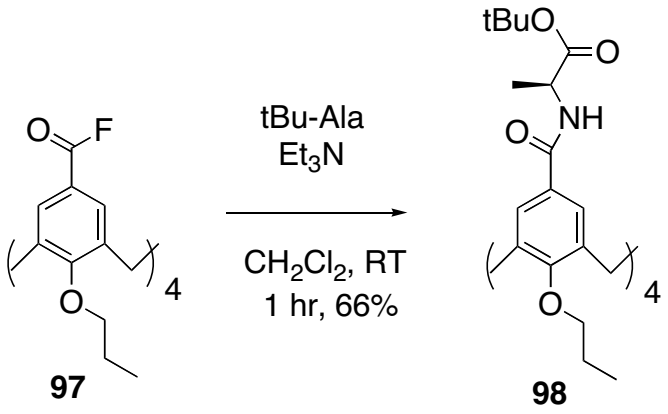
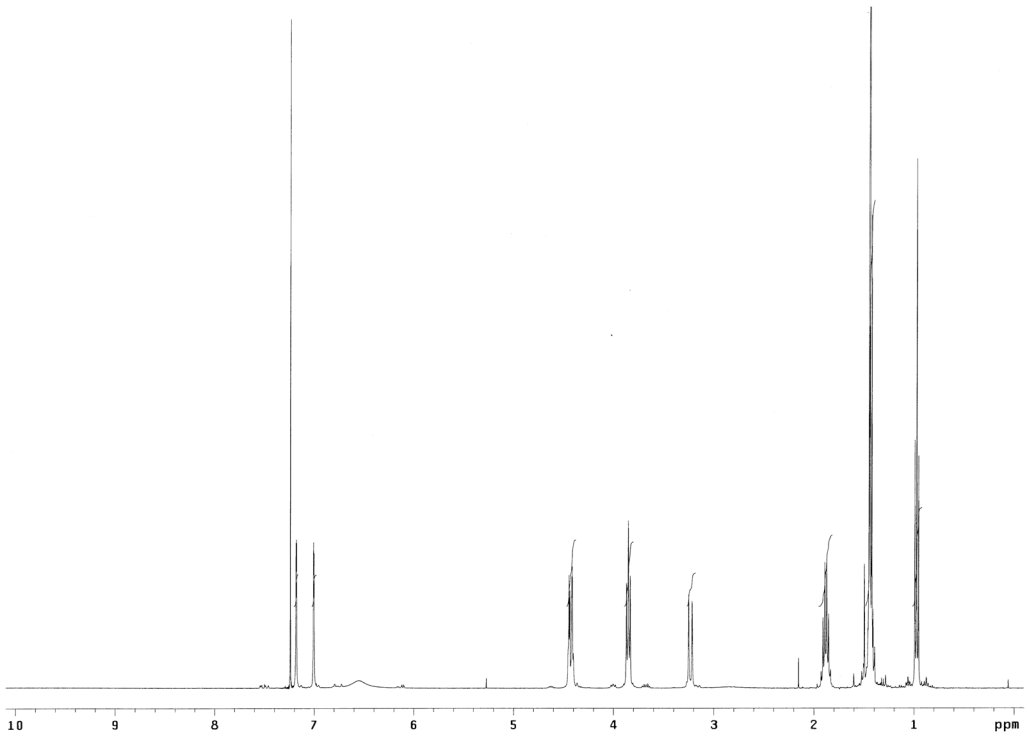


Synthesis of Tetra-*t*-butylalaninotetrapropoxycalix[4]arene 98

t-Butyl-alanine hydrochloride (704 mg, 12 eq) was dissolved in methylene chloride (4 mL) in a round bottom flask under nitrogen. Triethylamine (0.5 mL, 12 eq) was added to the reaction and stirred. Tetracarboxyfluoro-tetrapropoxycalix[4]arene **97** (250 mg, 1 eq) was then added to the reaction. The reaction was stirred at room temperature and monitored by TLC (1:1, hexane:EtOAc). After 1 hour, the reaction was washed with saturated ammonium chloride and then brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by column chromatography (CH_2Cl_2 then 99:1, CH_2Cl_2: MeOH) yielding a yellow, fluffy solid (273 mg, 66%). M.P. = 118 °C (dec.); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.18 (s, 4 H), δ 7.00 (s, 4 H), δ 4.43 (m, 8 H), δ 3.85 (t. 8 H, J = 7.5 Hz), δ 3.23 (d, 4 H, J = 13.6 Hz), δ 1.88 (m, 8 H, J = 7.7 Hz), δ 1.44 (m, 48 H), δ 0.97 (t, 12 H, J = 7.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.2, 166.6, 159.0, 134.7, 134.4, 128.3, 128.0, 126.6, 81.5, 77.0, 49.2, 31.1, 28.1, 23.2, 18.4, 10.4; HRMS (FAB) Calcd. for $C_{72}H_{101}N_4O_{16}$ (M^{+1}): m/z = 1277.72126 Found: m/z = 1277.72060.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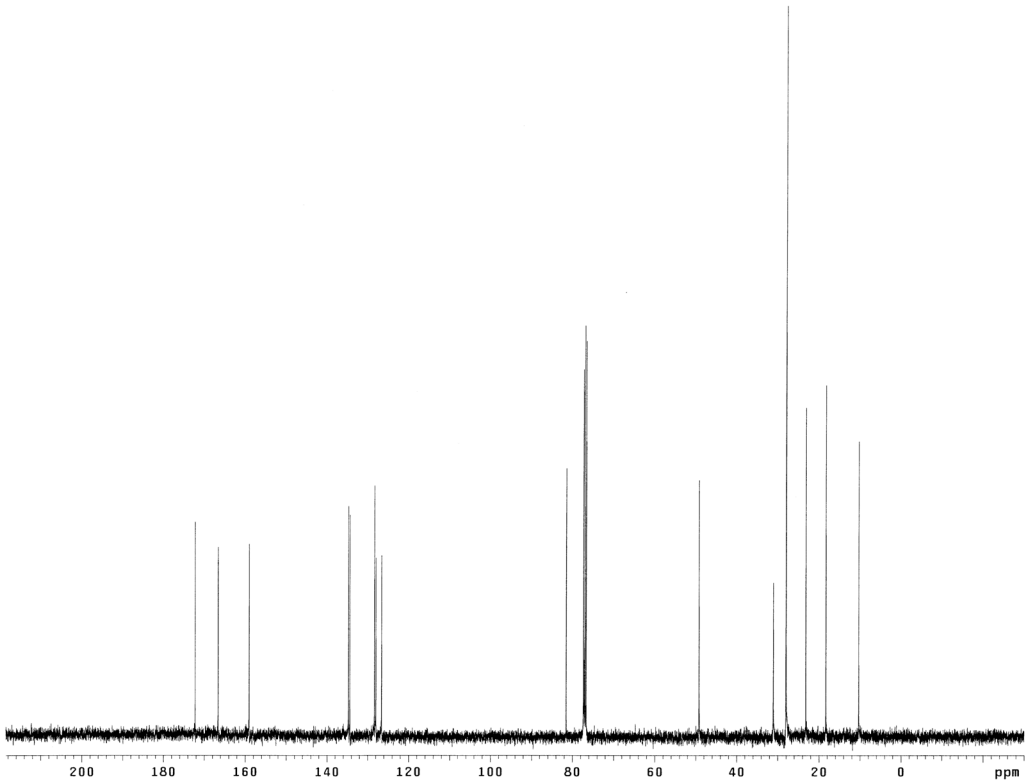
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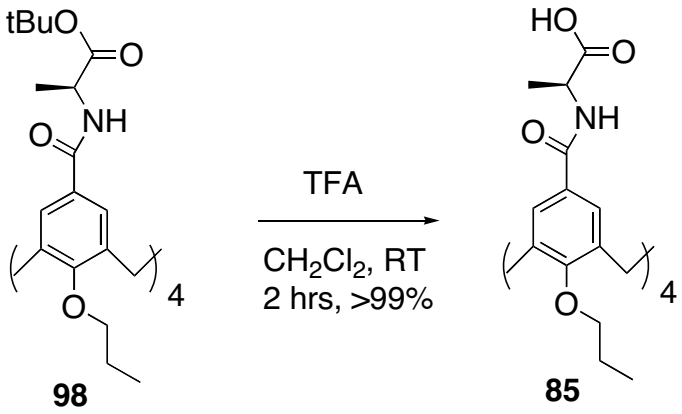
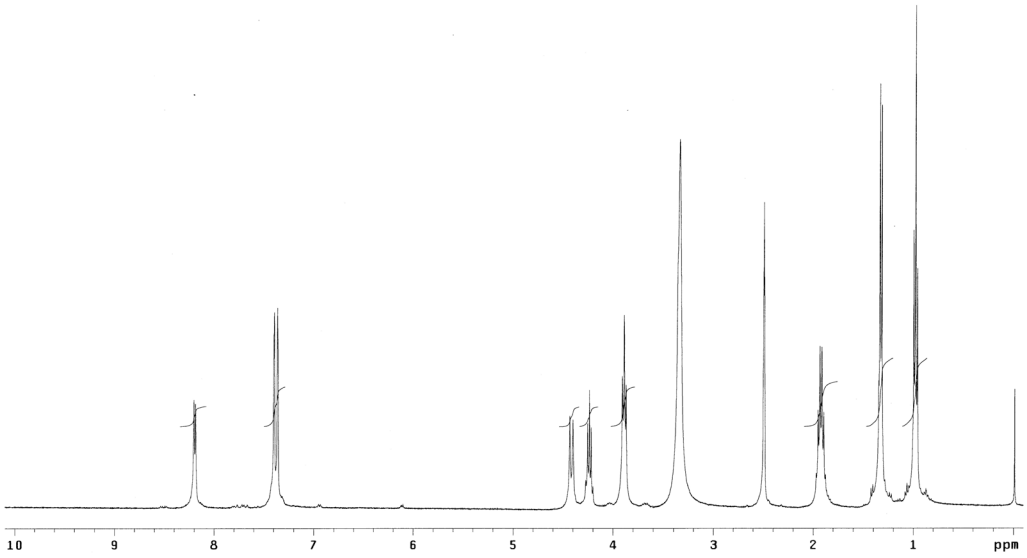


Synthesis of Tetra-alaninotetrapropoxycalix[4]arene 85

Tetra-*t*-butylalaninotetrapropoxycalix[4]arene **98** (30 mg, 1 eq) was dissolved in methylene chloride (0.95 mL) in a round bottom flask under nitrogen. Trifluoroacetic acid (0.05 mL) was added to the reaction. The reaction was stirred at room temperature and monitored by TLC (1:1, hexane:EtOAc). After 2 hours, the solvent was removed *in vacuo* yielding a fine, white solid (30 mg, >99%). M.P. = 218 °C (dec.); ^{1}H NMR (400 MHz DMSO-*d*6): δ 8.19 (d, 4 H, *J* = 6.8 Hz), δ 7.36 (s, 4 H), δ 7.39 (s, 4 H), δ 4.42 (d, 4 H, 12.8 Hz), δ 4.24 (m, 4 H, *J* = 7.0 Hz), δ 3.89 (t. 8 H, *J* = 7.6 Hz), δ 1.92 (m, 8 H, *J* = 7.6 Hz), δ 1.32 (d, 12 H, *J* = 6.8 Hz), δ 0.98 (t, 12 H, *J* = 7.6 Hz); ^{13}C NMR (400 MHz, DMSO-*d*6): δ 174.6, 166.1, 158.7, 134.2, 134.0, 128.5, 128.4, 127.9, 76.8, 48.4, 30.7, 22.9, 17.0,10.4; HRMS (FAB) Calcd. for $C_{56}H_{69}N_4O_{16}$ (M^{+1}): *m*/*z* = 1053.47086 Found: *m*/*z* = 1053.47058.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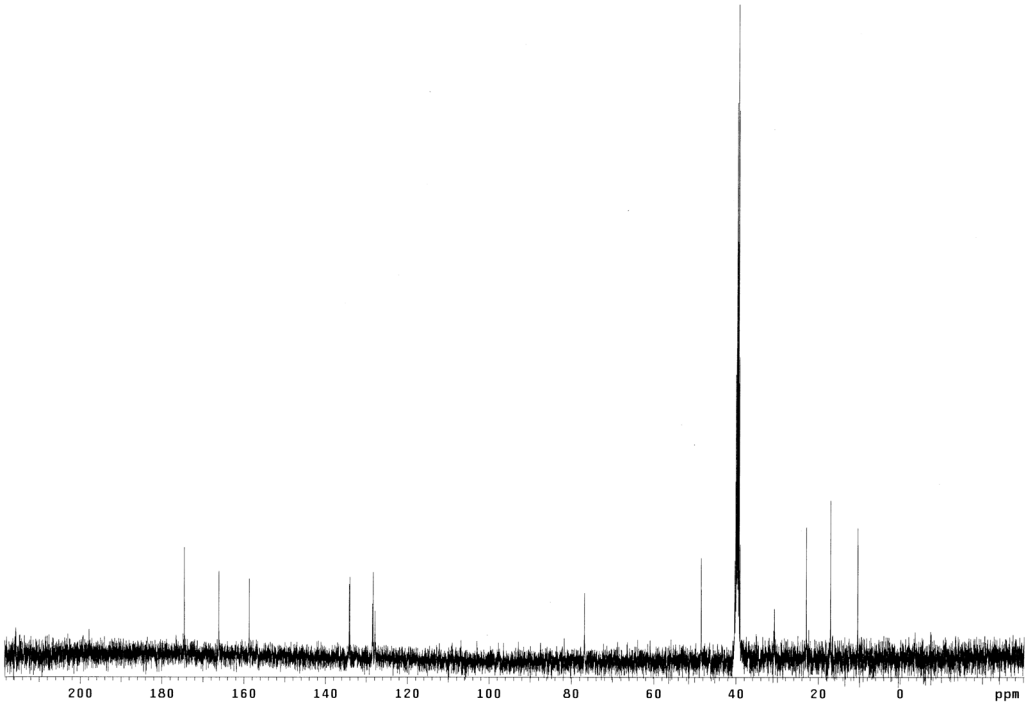
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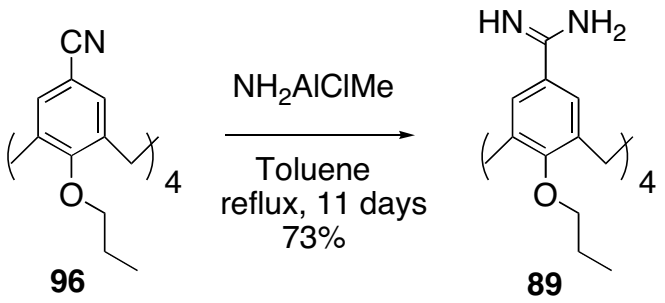
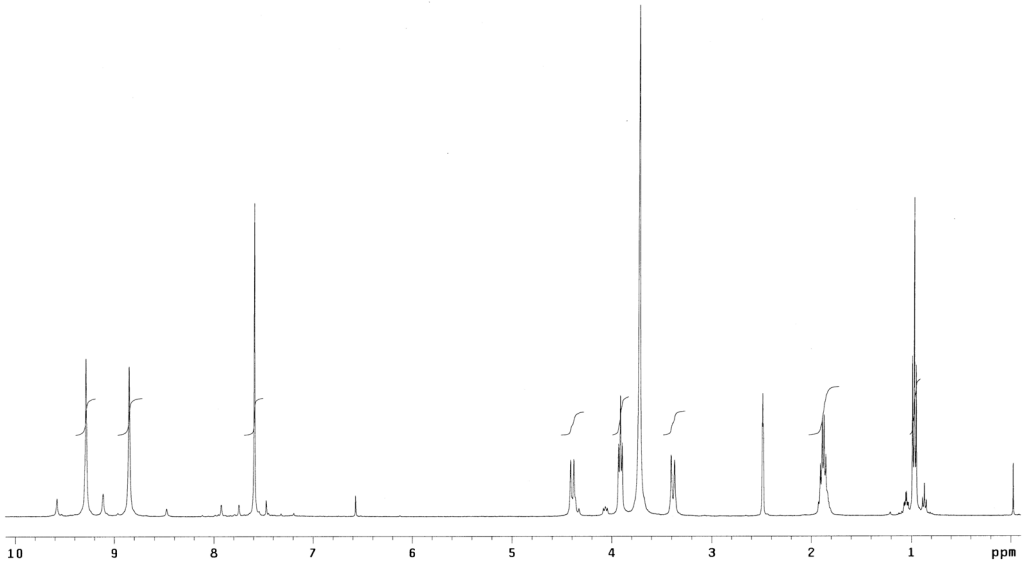


Synthesis of Tetra-amidinotetrapropoxycalix[4]arene 89[5]

Ammonium chloride (306 mg, 40 eq) was dissolved in dichloroethane (4 mL) in a round bottom flask under nitrogen. The reaction was cooled to 0 °C and trimethyl aluminum (2 M, 2.9 mL, 40 eq) was added dropwise. When the bubbling stopped (~2 hours), tetranitrilocalix[4]arene **96** (100 mg, 1 eq) dissolved in dichloroethane (2 mL) was added to the reaction. The reaction was warmed to room temperature and the refluxed for 11 days. The reaction was then cooled to 0 °C and quenched with ice (10 g) and methanol (15 mL). The solution was filtered over celite and the solid was washed with methanol and deionized water. The combined filtrates were concentrated *in vacuo*. Hydrochloric acid (3 N, 40 mL) was added and some of the solid dissolved. The remaining solid was removed by filtration and the filtrate was concentrated *in vacuo*. NMR of the solid showed that it was product (96 mg, 73%). M.P. > 320 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 9.29 (s, 6 H), δ 8.85 (s, 6 H), δ 7.59 (s, 8 H), δ 4.40 (d, 4 H, 13.2 Hz), δ 3.91 (t, 8 H, J = 7.6 Hz), δ 3.39 (d. 4 H, J = 13.6 Hz), δ 1.88 (m, 8 H, J = 7.2 Hz), δ 0.97 (t, 12 H, J = 7.2 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 164.0, 160.5, 134.7, 129.1, 121.1, 76.9, 30.2, 22.8, 10.1; HRMS (FAB) Calcd. for $C_{44}H_{57}N_8O_4$ (M^{+1}): m/z = 761.45028 Found: m/z = 761.45213.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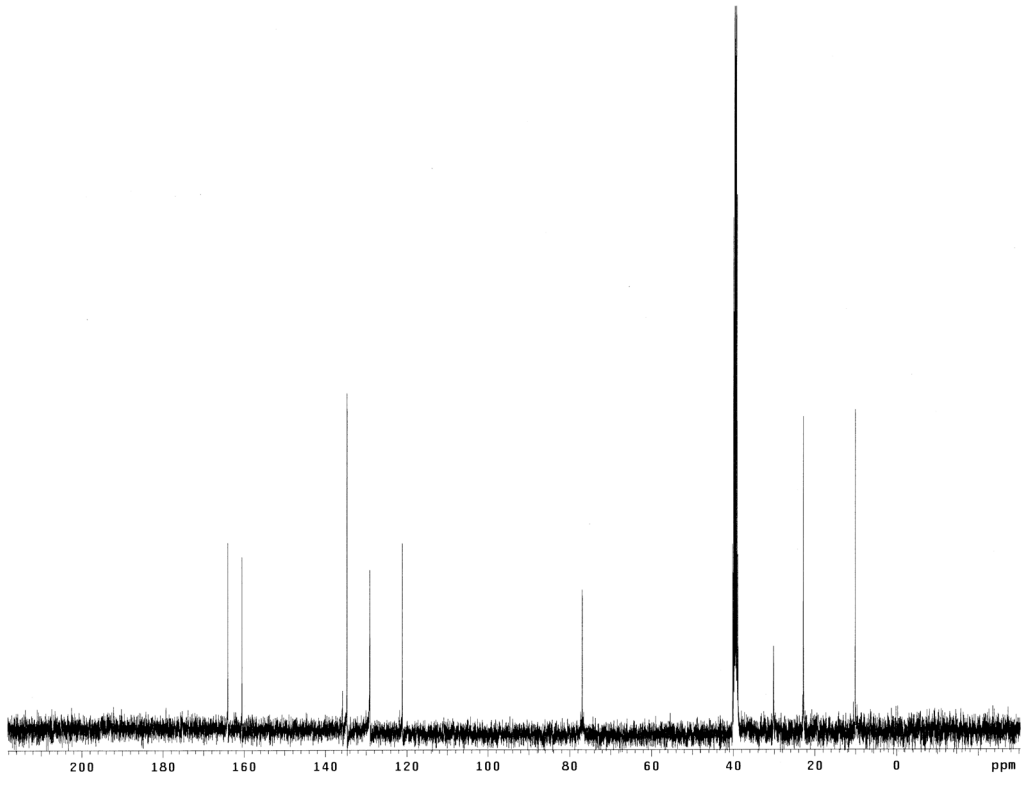
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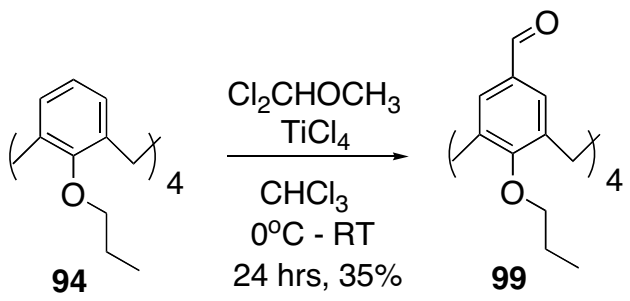
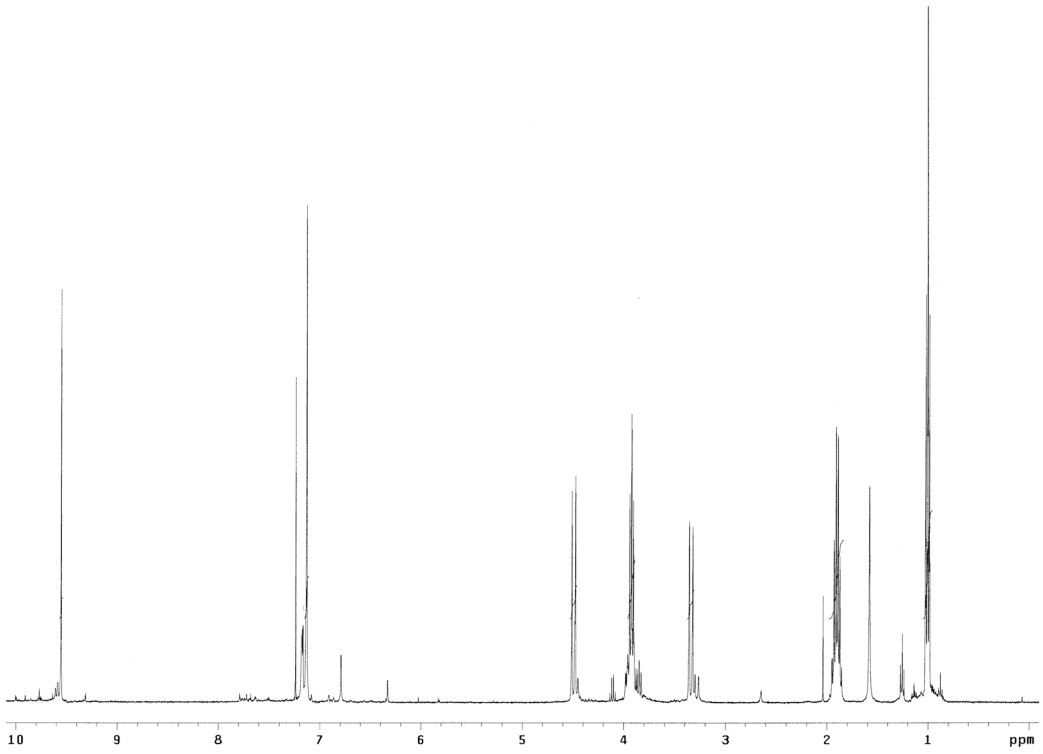


Synthesis of Tetraformyltetrapropoxycalix[4]arene 99[6]

1,1-Dichlorodimethylether (0.11 mL, 14 eq) and titanium chloride (0.15 mL, 16 eq) were dissolved in chloroform (3 mL) in a round bottom flask under nitrogen. The reaction was cooled to 0 °C and tetrapropoxycalix[4]arene **94** (50 mg, 1 eq) was added dropwise to the solution. The reaction was stirred for 1 hour and then warmed to room temperature and stirred overnight. The reaction was then quenched with deionized water. The organic layer was separated and washed with more deionized water. The organic layer was then dried over magnesium sulfate and concentrated *in vacuo*. The product (31 mg, 52%) was purified by column chromatography (8:2, hexane:EtOAc). M.P. 270-274 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 9.56 (s, 4 H), δ 7.13 (s, 8 H), δ 4.49 (d, 4 H, *J* = 13.6 Hz), δ 3.92 (t. 8 H, *J* = 7.4 Hz), δ 3.34 (d, 4 H, *J* = 14.0 Hz), δ 1.90 (m, 8 H, *J* = 7.6 Hz), δ 1.01 (t, 12 H, *J* = 7.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.0, 161.7, 135.4, 131.2, 130.1, 77.2, 31.0, 23.4, 10.4; HRMS (FAB) Calcd. for $C_{44}H_{49}O_8$ (M^{+1}): *m/z* = 705.34274 Found: *m/z* = 705.34864.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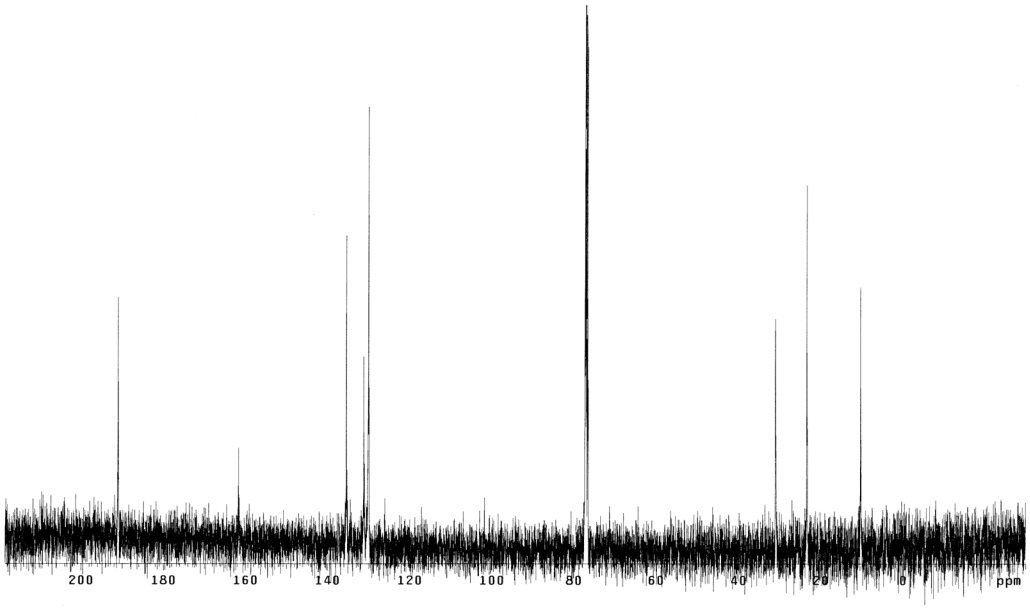
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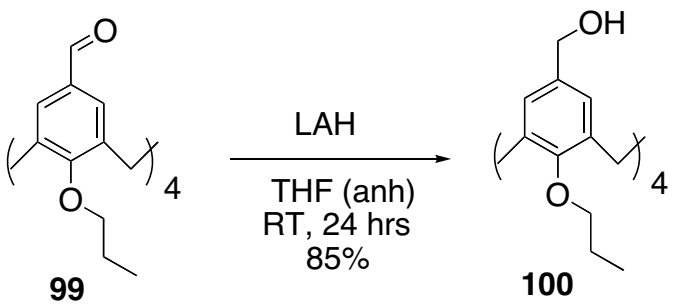
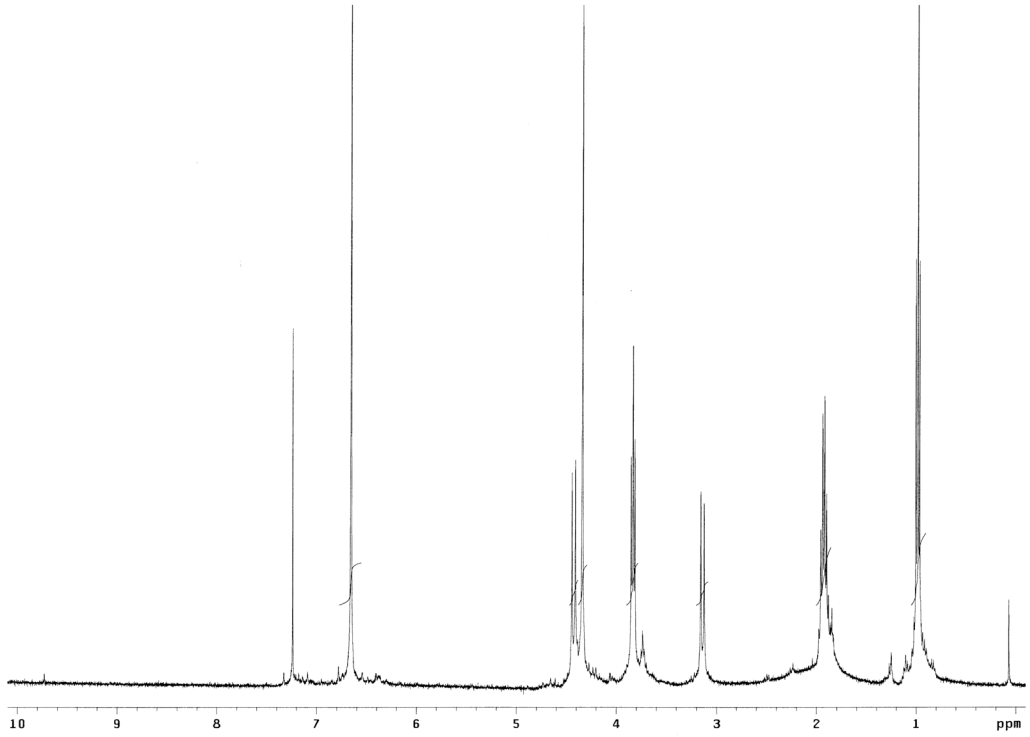


Synthesis of Tetrahydroxymethyltetrapropoxycalix[4]arene 100

Tetraformyltetrapropoxycalix[4]arene **99** (833 mg, 1 eq) was dissolved in anhydrous THF (30 mL) in a round bottom flask under nitrogen. Lithium aluminum hydride (540 mg, 12 eq) was added and stirred at room temperature overnight. The reaction was then quenched with distilled water. The solution was then acidified with 1N HCl and extracted with methylene chloride. The organic layer was separated and washed with deionized water and brine. The organic layer was then dried over magnesium sulfate and concentrated *in vacuo* yielding hydroxymethylcalix[4]arene (685 mg, 81%). M.P. 250-253 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 6.66 (s, 8 H), δ 4.43 (d, 4 H, *J* = 13.2 Hz), δ 4.34 (s, 8 H), δ 3.83 (t. 8 H, *J* = 7.4 Hz), δ 3.14 (d, 4 H, *J* = 13.2 Hz), δ 1.93 (m, 8 H, *J* = 7.2 Hz), δ 0.99 (t, 12 H, *J* = 7.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 155.8, 134.8, 134.4, 126.9, 76.9, 64.8, 31.1, 23.3, 10.4; HRMS (FAB) Calcd. for $C_{44}H_{56}O_8$ (M^+): *m*/*z* = 712.39752 Found: *m*/*z* = 712.40052.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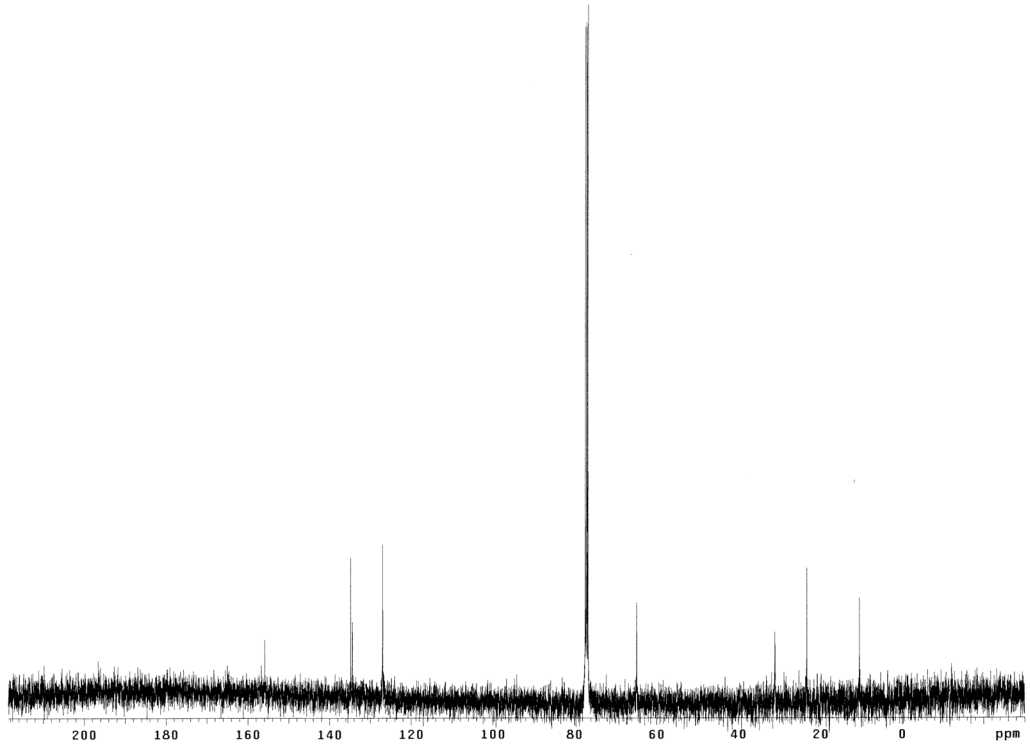
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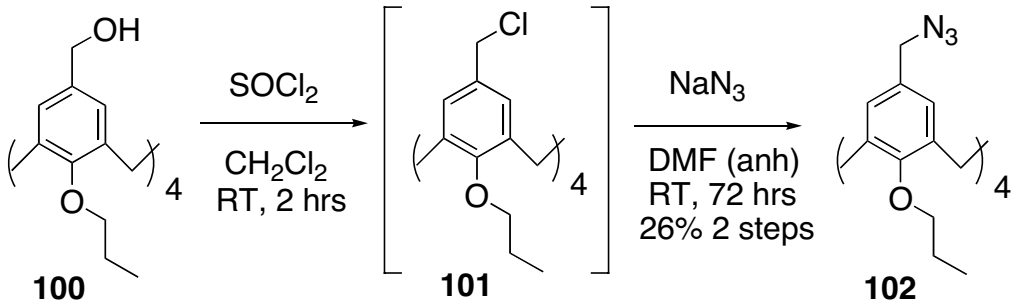
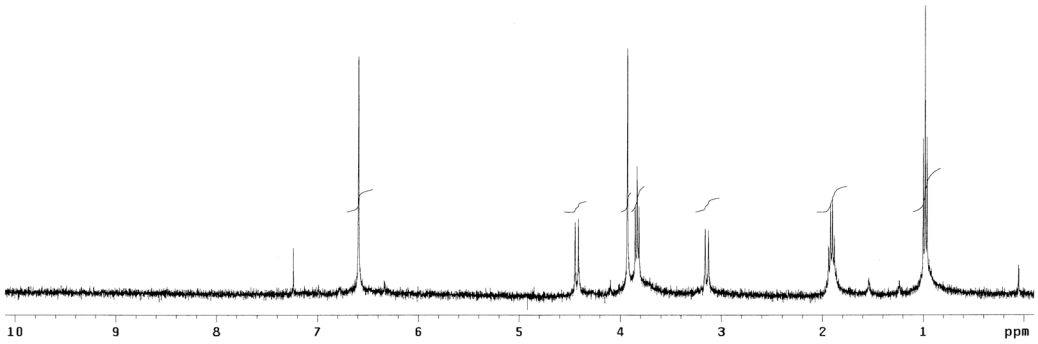


Synthesis of Tetra-azidotetrapropoxycalix[4]arene 102[7]

Tetrahydroxymethyltetrapropoxycalix[4]arene **100** (685 mg, 1 eq) was dissolved in methylene chloride (20 mL) in a round bottom flask under nitrogen. Thionyl chloride (1.4 mL, 20 eq) was added and stirred at room temperature for two hours. The reaction was then concentrated *in vacuo* and redissolved in anhydrous DMF (20 mL). Sodium azide (625 mg, 10 eq) was then added and stirred over the weekend at room temperature. The reaction was then quenched with 1N HCl. The solution was then extracted with methylene chloride. The organic layer was washed with deionized water until all of the DMF was removed. The organic layer was then dried over magnesium sulfate and concentrated *in vacuo*. The product was then purified through a silica plug yielding azidomethylcalix[4]arene (200 mg, 26%). M.P. = 200-202 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 6.59 (s, 8 H), δ 4.43 (d, 4 H, *J* = 13.2 Hz), δ 3.93 (s, 8 H), δ 3.83 (t. 8 H, *J* = 7.6 Hz), δ 3.14 (d, 4 H, *J* = 13.2 Hz), δ 1.91 (m, 8 H, *J* = 7.6 Hz), δ 0.98 (t, 12 H, *J* = 8.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.5, 135.1, 128.6, 128.5, 76.9, 54.2, 30.8, 23.2, 10.2.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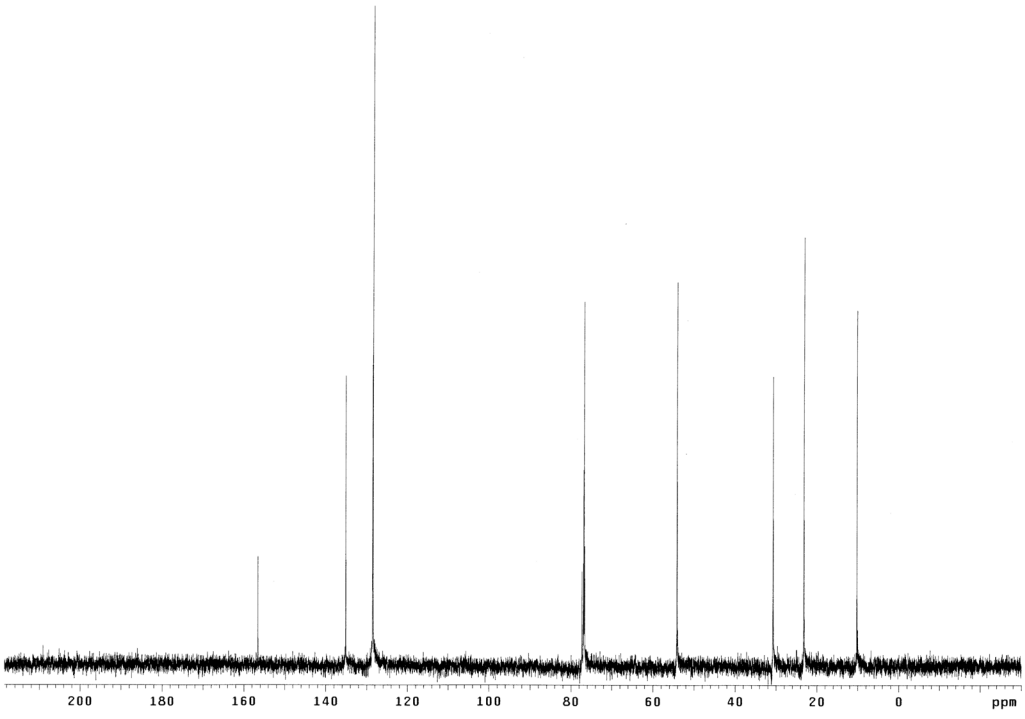
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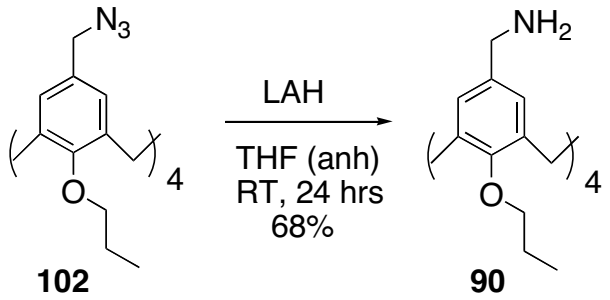
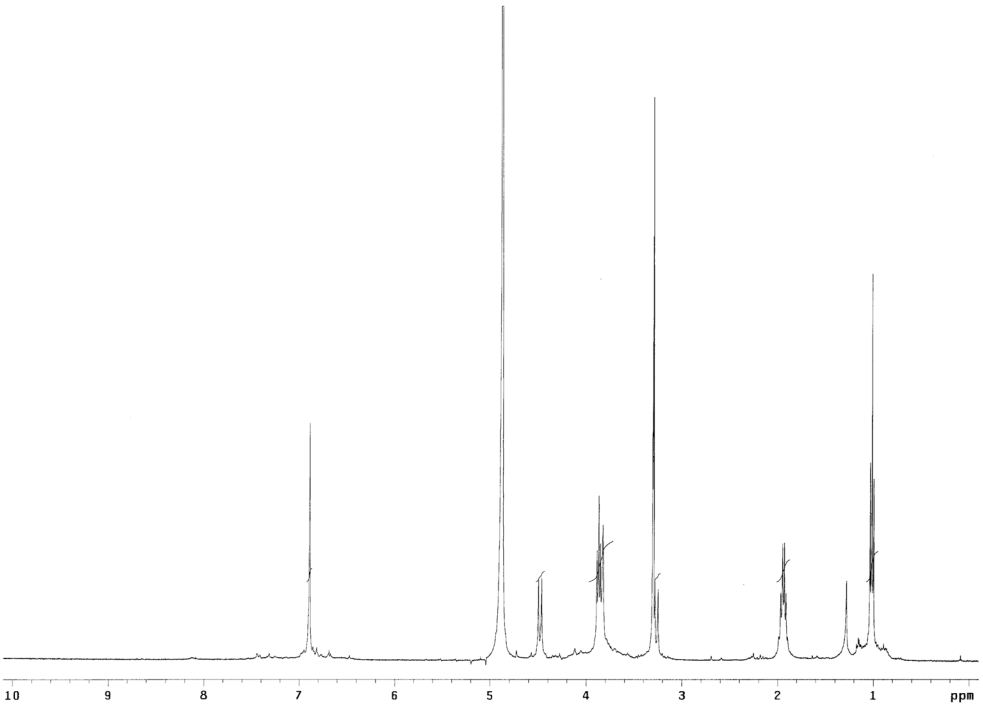


102 **90**

Synthesis of Tetra-aminomethyltetrapropoxycalix[4]arene 90[8]

Azidomethyltetrapropoxycalix[4]arene **102** (50 mg, 1 eq) was dissolved in anhydrous THF (4 mL) in a round bottom flask under nitrogen. Lithium aluminum hydride (28 mg, 12 eq) was added and stirred overnight at room temperature. The reaction was then quenched with distilled water and extracted with methylene chloride. The organic layer was washed with deionized water and brine. An emulsion formed that separated upon addition of KOH (5% in water). The organic layer was then dried over magnesium sulfate and concentrated *in vacuo* yielding aminomethylcalix[4]arene (30 mg, 68%). The product was characterized by NMR. M.P. 240 °C (dec.); ^{1}H NMR (400 MHz CD_3OD): δ 6.89 (s, 8 H), δ 4.48 (d, 4 H, *J* = 13.2 Hz), δ 3.87 (t. 8 H, *J* = 7.2 Hz), δ 3.83 (s, 8 H), δ 3.27 (d, 4 H, *J* = 13.2 Hz), δ 1.94 (m, 8 H, *J* = 7.2 Hz), δ 1.02 (t, 12 H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, CD_3OD): δ 158.4, 136.8, 130.6, 128.1, 78.2, 44.0, 31.7, 24.4, 10.8; HRMS (FAB) Calcd. for $C_{44}H_{61}N_4O_4$ (M^{+1}): *m/z* = 709.46928 Found: *m/z* = 709.46362.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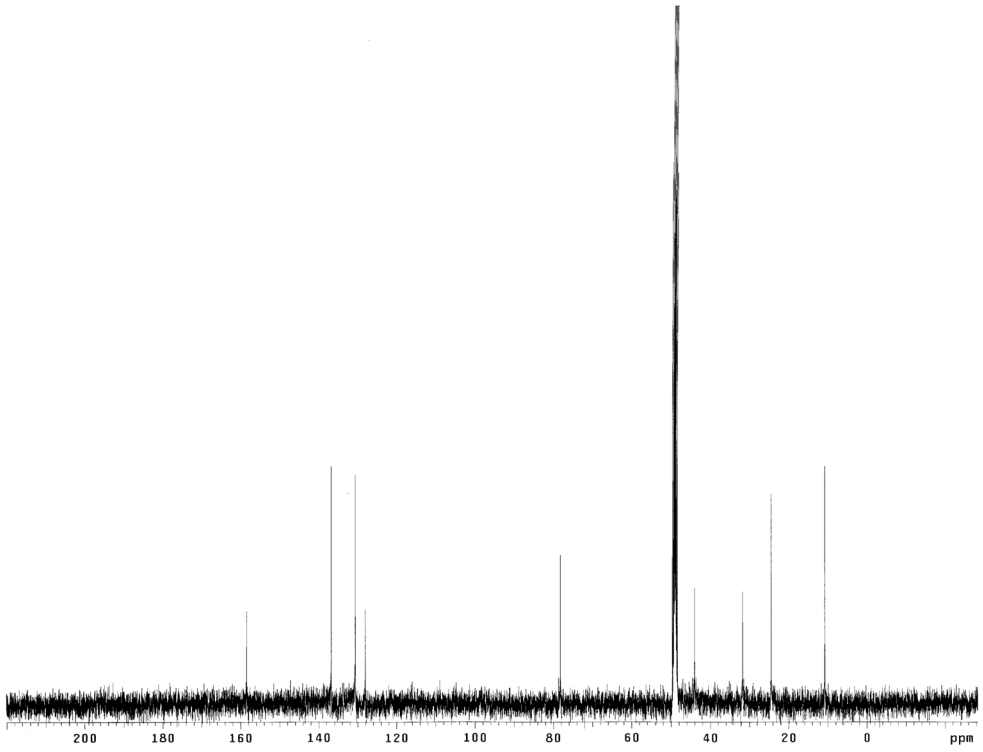
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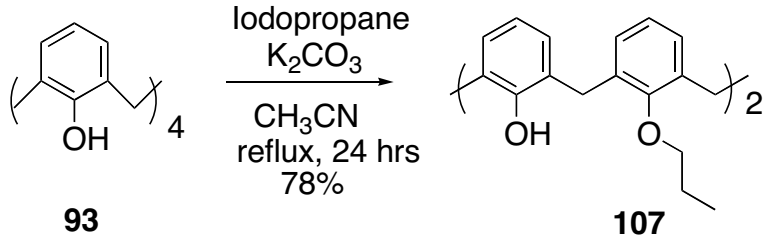
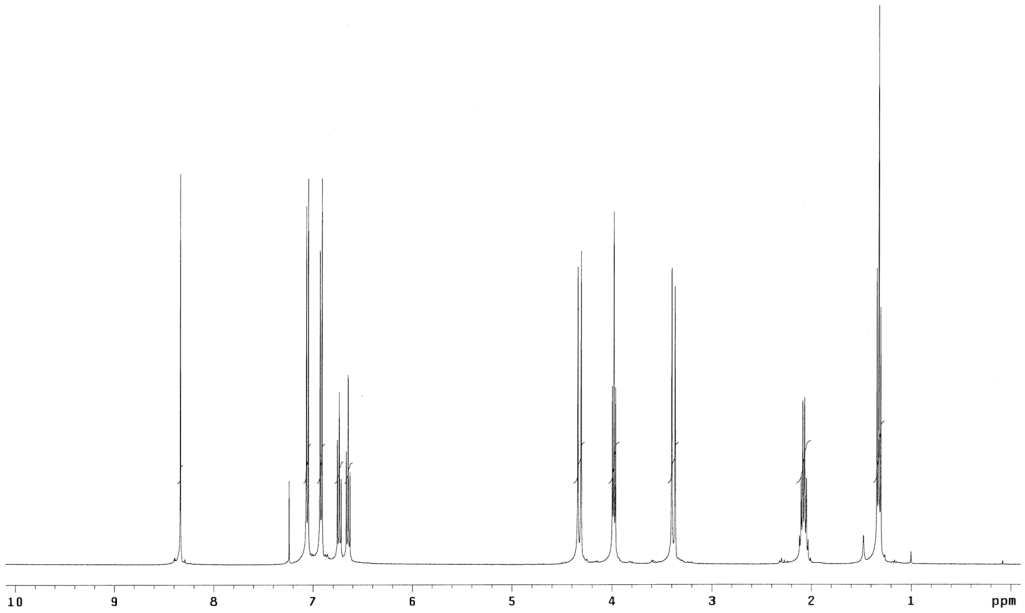


93 **107**

Synthesis of Dipropoxycalix[4]arene 107[9, 10]

Calix[4]arene **93** (27 g, 1 eq) was placed in a round bottom flask with acetonitrile (900 mL) under nitrogen. Potassium carbonate (2 eq) and iodopropane (4 eq) were added to the reaction and refluxed. After 24 hours, the reaction was concentrated to dryness and redissolved in methylene chloride and 1 N HCl. The organic layer was separated and washed with 1 N HCl, deionized water, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The product, a white solid, was then recrystallized from methylene chloride and methanol (25 g, 78% yield). M.P. 260 °C (dec.); ^{1}H NMR (400 MHz $CDCl_3$): δ 8.34 (s, 2 H), δ 7.06 (d, 4 H, *J* = 7.6 Hz), δ 6.92 (d, 4 H, *J* = 7.6 Hz), δ 6.74 (t, 2 H, *J* = 7.2 Hz), δ 6.65 (t, 2 H, *J* = 7.2 Hz), δ 4.33 (d, 4 H, *J* = 12.8 Hz), δ 3.98 (t, 4 H, *J* = 6.0 Hz), δ 3.38 (d, 4 H, *J* = 12.8 Hz), δ 2.09-2.06 (m, 4 H), δ 1.32 (t, 6 Hz, *J* = 7.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 153.3, 151.8, 133.5, 128.9, 128.4, 128.1, 125.3, 118.9, 78.3, 31.4, 23.5, 10.9; HRMS (FAB) Calcd. for $C_{34}H_{36}O_4$ (M^+): *m*/*z* = 508.26136 Found: *m*/*z* = 508.26319.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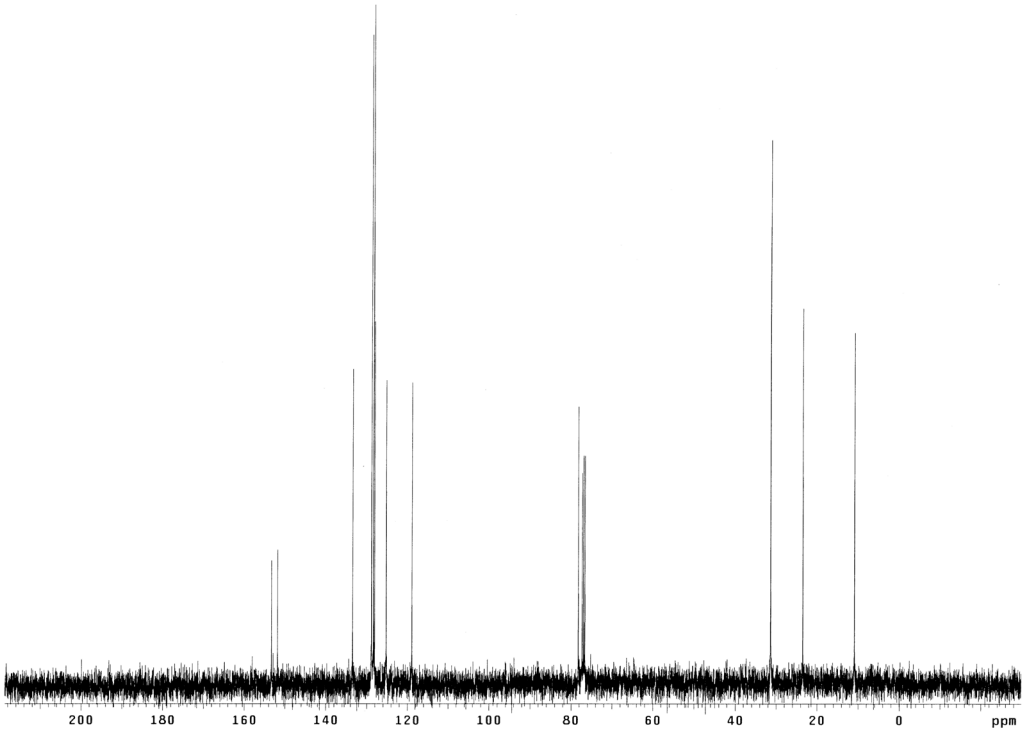
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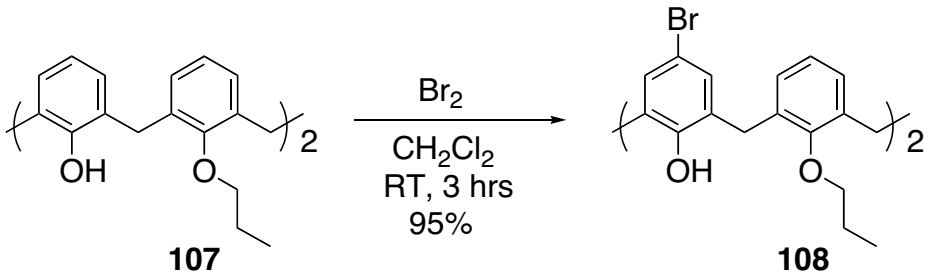
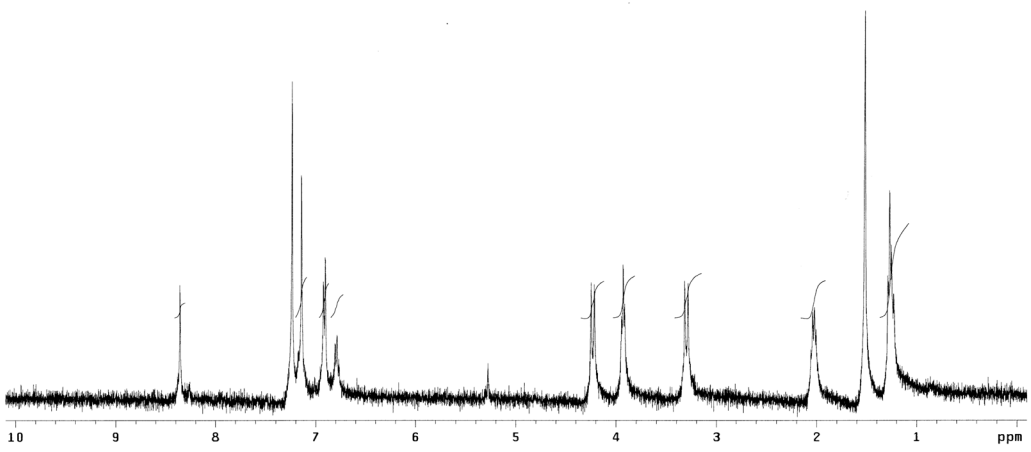


107 **108**

Synthesis of Dibromodipropoxycalix[4]arene 108

Dipropoxycalix[4]arene **107** (4.7 g, 1 eq) was dissolved in methylene chloride (1 L) in a round bottom flask under nitrogen. Bromine (3 eq) was added and stirred. The product precipitates upon formation. After 3 hours, the product, a white solid, was removed by filtration and washed with methylene chloride (5.8 g, 95% yield). M.P. > 320 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 8.36 (s, 2 H), δ 7.15 (s, 4 H), δ 6.92 (d, 4 H, *J* = 7.2 Hz), δ 6.79 (t, 2 H, *J* = 7.2 Hz), δ 4.23 (d, 4 H, *J* = 12.8 Hz), δ 3.93 (t, 4 H, *J* = 6.0 Hz), δ 3.30 (d, 4 H, *J* = 14.0 Hz), δ 2.05-1.95 (m, 4 H), δ 1.27 (t, 6 Hz, *J* = 7.2 Hz); HRMS (EI) Calcd. for $C_{34}H_{34}Br_2O_4$ (M^+): *m*/*z* = 664.0824 Found: *m*/*z* = 664.0864.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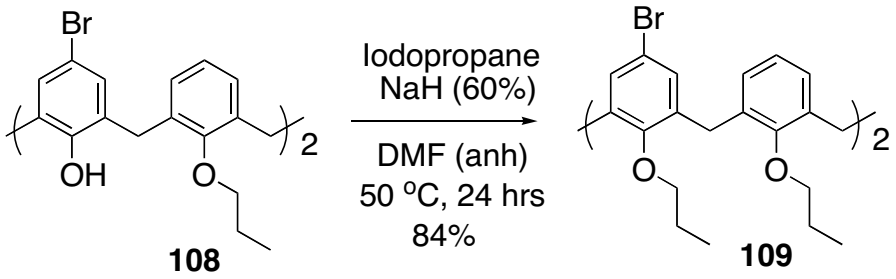
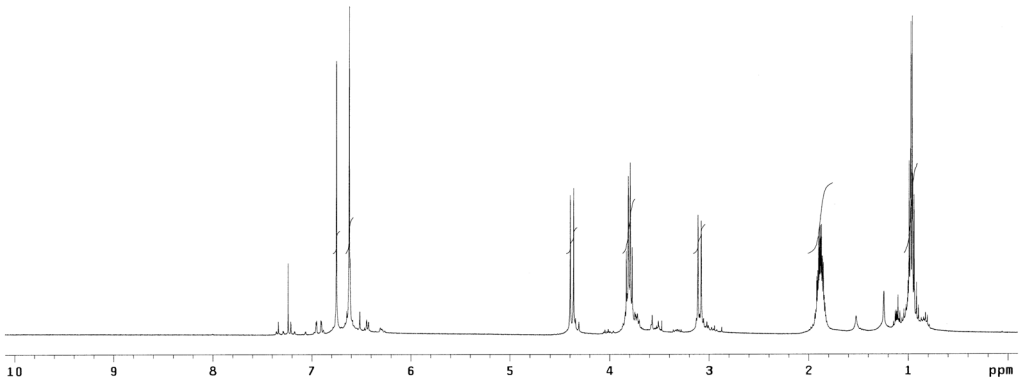


Synthesis of Dibromotetrapropoxycalix[4]arene 109

Dibromodipropoxycalix[4]arene **108** (5.8 g, 1 eq) was dissolved in anhydrous DMF in a round bottom flask under nitrogen. Sodium hydride (4 eq) was added to the reaction and stirred for 30 minutes. Iodopropane (6 eq) was added and the reaction was heated to 50 °C and stirred overnight. The reaction was monitored by TLC (5:1, hexane:EtOAc). The reaction was quenched with deionized water and 1 N HCl. The product was extracted with methylene chloride. The organic layer was washed with deionized water until all of the DMF was removed. The organic layer was then washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The brown oil was triturated with methanol overnight yielding a white solid (5.2 g, 86% yield). M.P. = 226-230 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 6.75 (s, 4 H), δ 6.62 (s, 6 H), δ 4.38 (d, 4 H, *J* = 13.6 Hz), δ 3.80 (m, 8 H), δ 3.09 (d, 4 H, *J* = 13.6 Hz), δ 1.89-1.86 (m, 8 H), δ 0.97 (m, 12 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.3, 155.7, 137.2, 134.3, 130.7, 128.4, 122.4, 114.7, 76.9, 76.8, 30.8, 23.2, 10.2; HRMS (FAB) Calcd. for $C_{40}H_{46}Br_2O_4$ (M^+): *m*/*z* = 748.1763 Found: *m*/*z* = 748.1770.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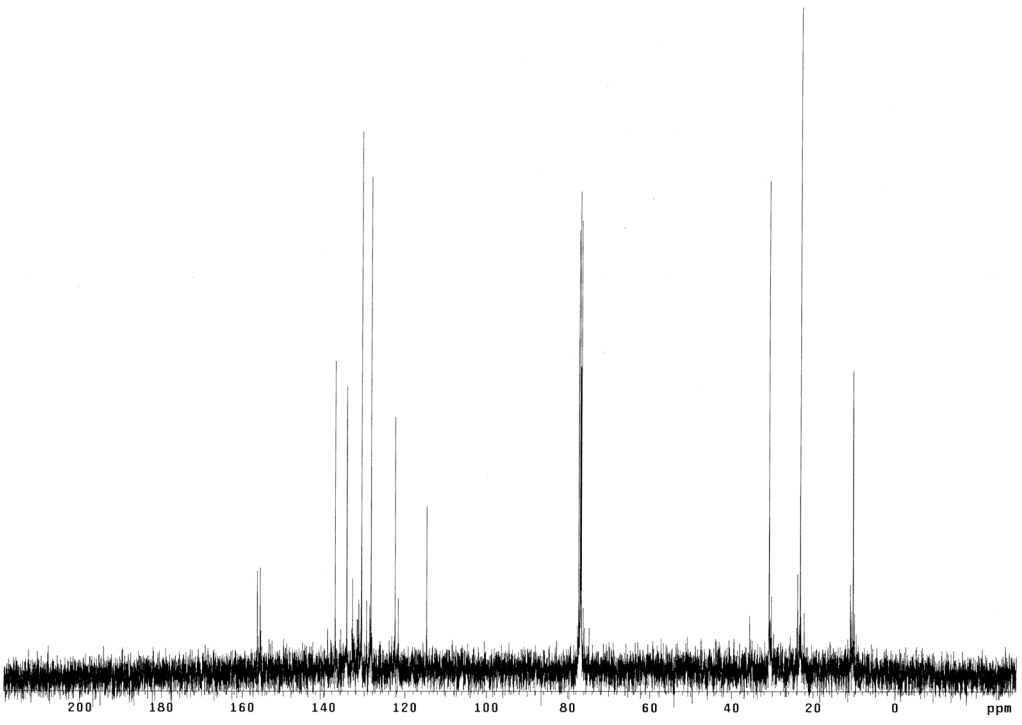
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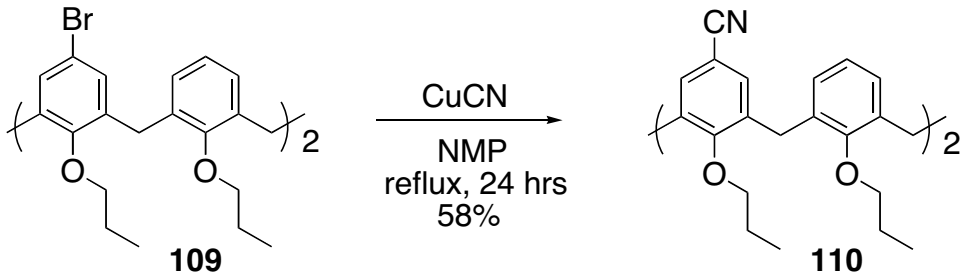
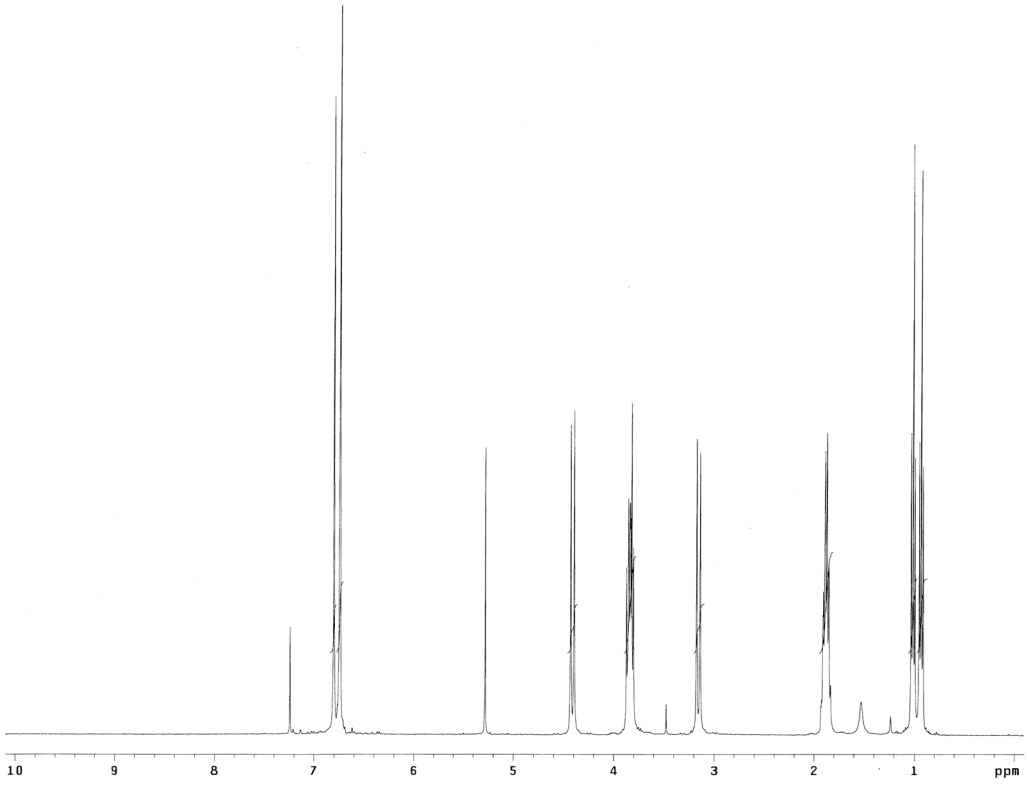


109 **110**

Synthesis of Dinitrilotetrapropoxycalix[4]arene 110[3]

Dibromotetrapropoxycalix[4]arene **109** (6.2 g, 1 eq) was dissolved in *N*-methylpyrrolidinone (300 mL) in a round bottom flask under nitrogen. Copper (I) cyanide (4 eq) was added and the reaction was refluxed overnight. After 24 hours, the reaction was cooled to 100 °C. Iron (III) chloride hexahydrate (4 eq) was dissolved in 1.6 M HCl (300 mL) and heated to 100 °C. The reaction was added to the iron chloride and stirred for 1 hour. The reaction was cooled to room temperature and filtered to remove the product. The product was washed with deionized water. The product was then dissolved in methylene chloride and precipitated out with methanol (brown solid, 3.1 g, 58% yield). M.P. = 299-302 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 6.80 (s, 4 H), δ 6.74 (s, 6 H), δ 4.14 (d, 4 H, *J* = 13.6 Hz), δ 3.87-3.81 (m, 8 H), δ 3.16 (d, 4 H, *J* = 13.6 Hz), δ 1.90-1.85 (m, 8 H), δ 1.02 (t, 6 H, *J* = 7.2 Hz), δ 0.93 (t, 6 H, *J* = 7.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.7, 156.2, 136.0, 134.4, 131.8, 128.7, 122.8, 105.5, 77.2, 76.8, 30.8, 23.4, 23.2, 10.5, 10.2; HRMS (FAB) Calcd. for $C_{42}H_{46}N_2O_4$ (M^+): *m/z* = 642.3457 Found: *m/z* = 642.3466.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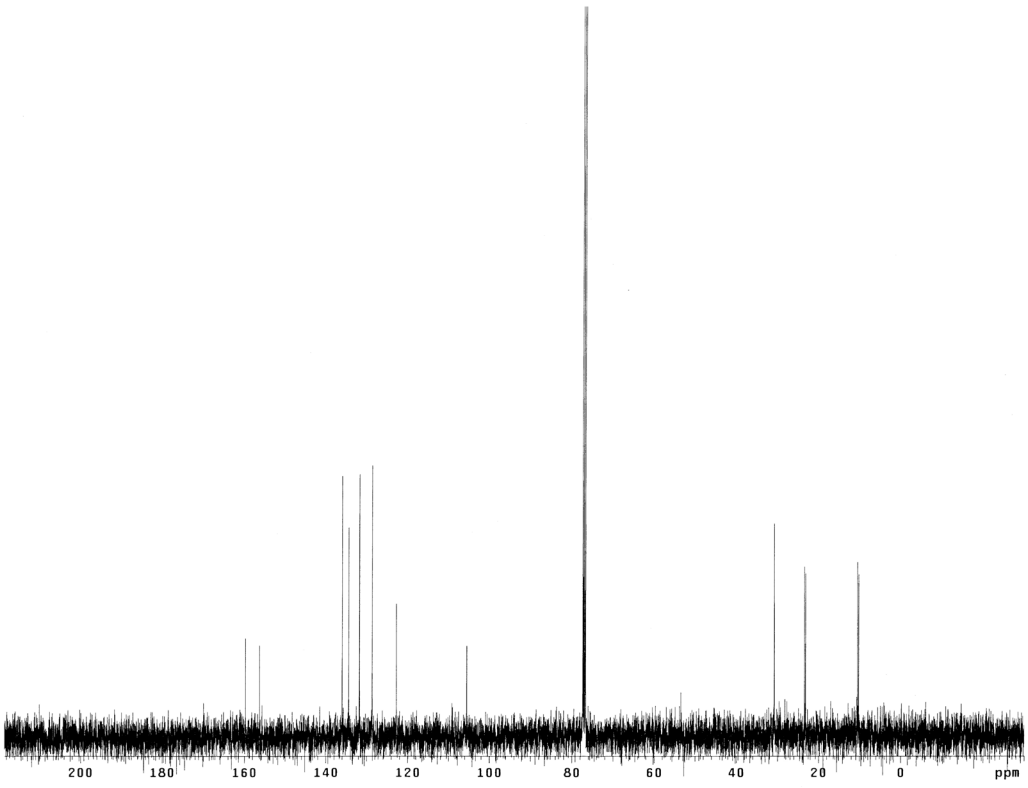
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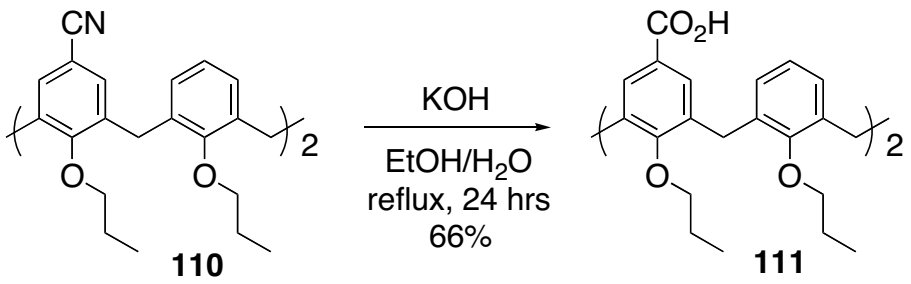
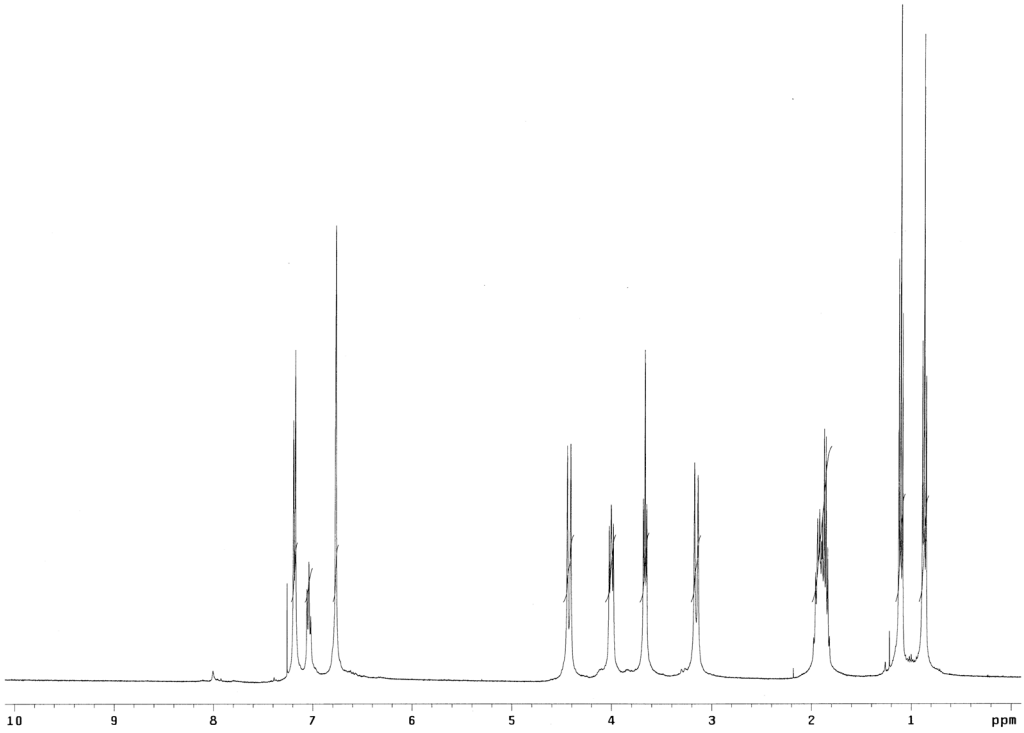


Synthesis of Dicarboxytetrapropoxycalix[4]arene 111

Dinitrilotetrapropoxycalix[4]arene **110** (10.7 g, 1 eq) was dissolved in ethanol (1.5 L) in a round bottom flask under nitrogen. Potassium hydroxide (1000 eq) was dissolved in deionized water (500 mL) and added to the reaction. The reaction was then refluxed overnight. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 24 hours, the reaction was quenched with concentrated HCl (~400 mL) and a white precipitate formed. The solid was removed by filtration and washed with deionized water. The solid was then dissolved in methylene chloride and dried over magnesium sulfate. The solution was then filtered and concentrated *in vacuo* yielding off white solid (7.5 g, 66% yield). M.P. > 320 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.18 (d, 4 H, J = 7.6 Hz), δ 7.04 (t, 2 H, J = 8.0 Hz), δ 6.77 (s, 4 H), δ 4.43 (d, 4 H, J = 13.6 Hz), δ 4.00 (t, 4 H, *J* = 8.0 Hz), δ 3.67 (t, 4 H, *J* = 6.4 Hz), δ 3.16 (d, 4 H, *J* = 13.6 Hz), δ 1.96-1.84 (m, 8 H), δ 1.11 (t, 6 H, *J* = 7.2 Hz), δ 0.88 (t, 6 H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.0, 159.7, 157.5, 136.5, 133.6, 129.6, 129.3, 123.1, 122.8, 76.8, 76.4, 30.8, 23.4, 22.9, 10.8, 9.7; HRMS (FAB) Calcd. for $C_{42}H_{48}O_8$ (M^+): *m/z* = 680.3349 Found: *m/z* = 680.3356.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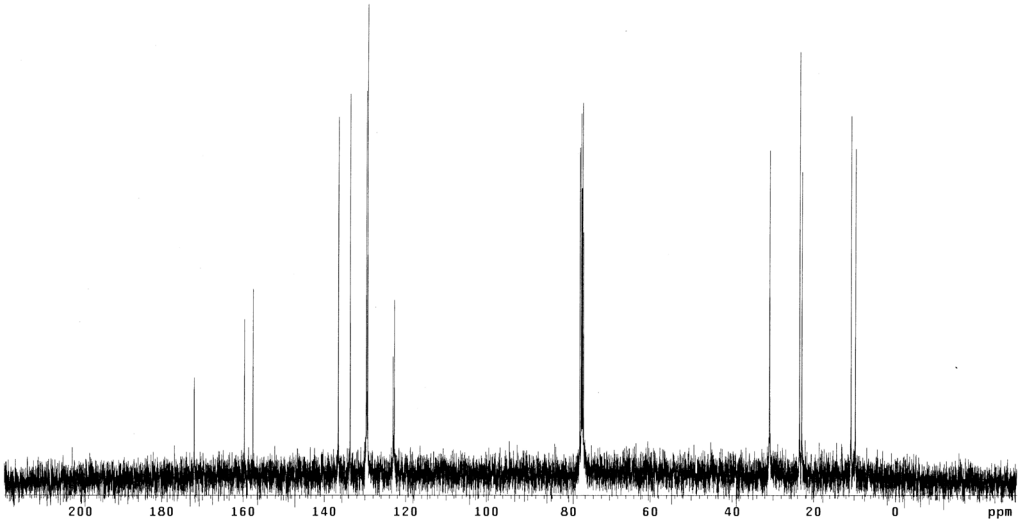
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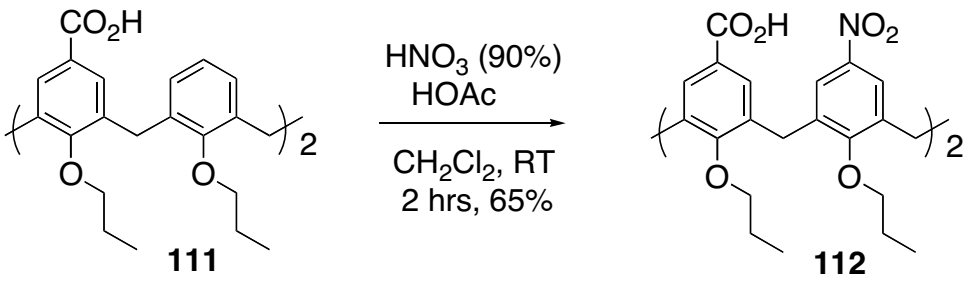
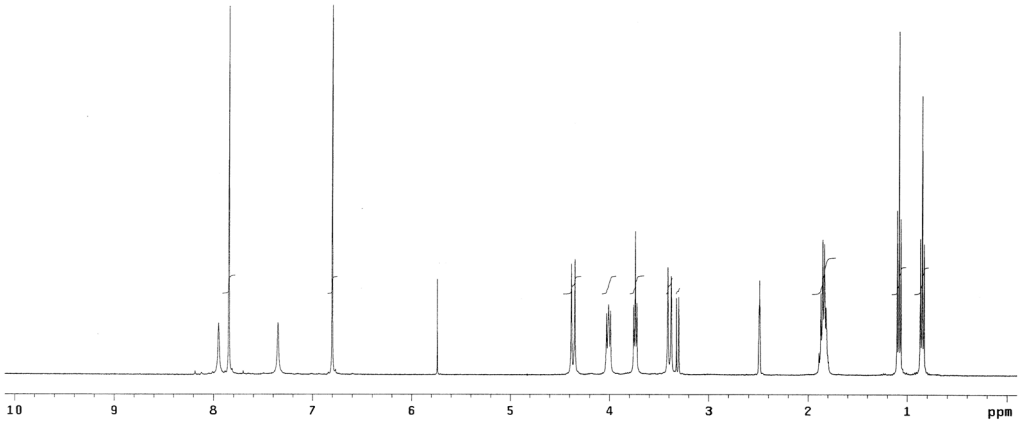


Synthesis of Dicarboxydinitrotetrapropoxycalix[4]arene 112[2]

Dicarboxytetrapropoxycalix[4]arene **111** (6 g, 1 eq) was dissolved in methylene chloride (750 mL) in a round bottom flask under nitrogen. Concentrated nitric acid (9% by volume) and glacial acetic acid (6% by volume) were mixed together and then added to the reaction. The reaction was stirred at room temperature for 2 hours and quenched with saturated sodium bicarbonate. The organic layer was washed with deionized water and brine. The organic layer was then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The solid was triturated in methanol overnight to remove some impurities yielding a yellow solid (4.4 g, 65% yield). M.P. = 298 °C (dec.); ^{1}H NMR (400 MHz DMSO-d_6): δ 7.95 (s, OH), δ 7.85 (s, 4 H), δ 7.35 (s, OH), δ 6.80 (s, 4 H), δ 4.37 (d, 4 H, J = 13.9 Hz), δ 4.01 (t, 4 H, J = 8.1 Hz), δ 3.74 (t, 4 H, J = 6.4 Hz), δ 3.40 (d, 4 H, J = 13.9 Hz), δ 1.82-1.87 (m, 8 H), δ 1.08 (t, 6 H, J = 7.3 Hz), δ 0.85 (t, 6 H, J = 7.3 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 146.5, 144.2, 127.5, 125.8, 32.7, 31.5; HRMS (FAB) Calcd. for $C_{42}H_{45}N_2O_{12}$ (M^{+1}): m/z = 769.2973 Found: m/z = 769.2938.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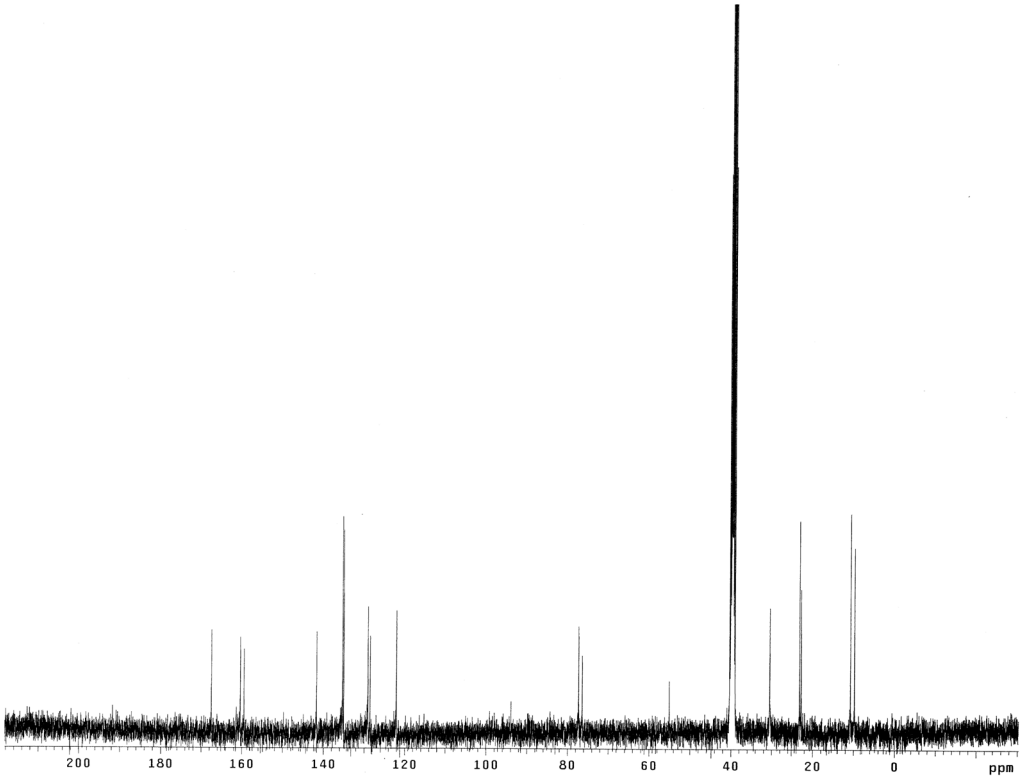
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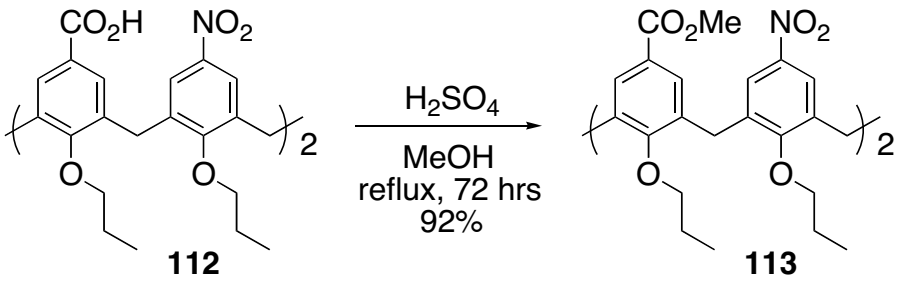
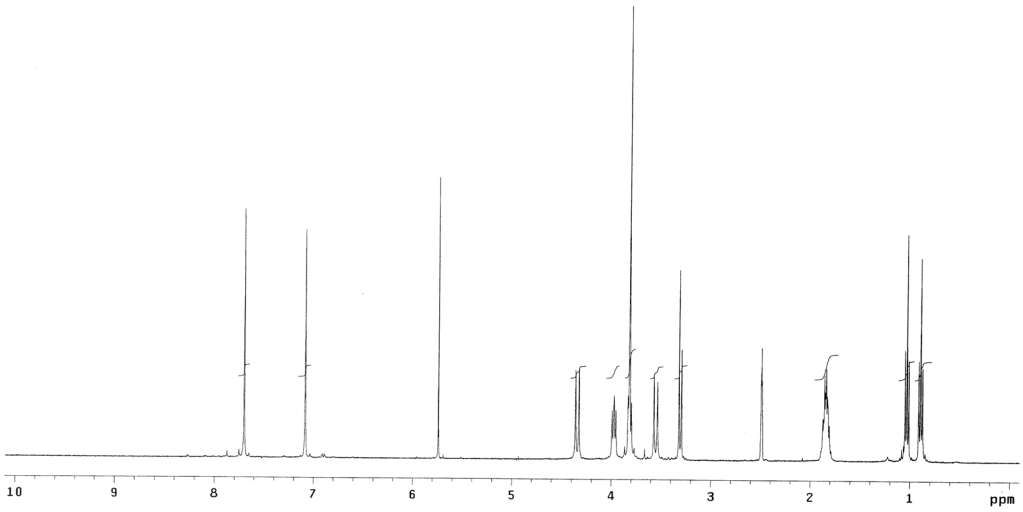


Synthesis of Dicarboxymethyldinitrotetrapropoxycalix[4]arene 113

Dicarboxydinitrotetrapropoxycalix[4]arene **112** (970 mg, 1 eq) was placed in a round bottom flask under nitrogen. Methanol (130 mL) was added and stirred. Sulfuric acid (20% by volume) was added and the reaction was refluxed. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 72 hours, the reaction was quenched with saturated sodium bicarbonate and extracted with methylene chloride. The organic layer was washed with more saturated sodium bicarbonate, deionized water, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. A brown crystalline solid was recovered (928 mg, 93% yield). M.P. = 115 °C (dec.); ^{1}H NMR (400 MHz DMSO-d_6): δ 7.70 (s, 4 H), δ 7.09 (s, 4 H), δ 4.34 (d, 4 H, J = 13.9 Hz), δ 3.97 (t, 4 H, J = 7.7 Hz), δ 3.82 (m, 10 H), δ 3.55 (d, 4 H, J = 13.7 Hz), δ 1.81-1.88 (m, 8 H), δ 1.03 (t, 6 H, J = 7.3 Hz), δ 0.90 (t, 6 H, J = 7.5 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.8, 161.1, 160.8, 141.6, 135.4, 135.3, 130.3, 123.8, 122.6, 77.2, 76.7, 55.1, 52.1, 30.1, 23.2, 22.9, 10.6, 10.0; HRMS (FAB) Calcd. for $C_{44}H_{51}N_2O_{12}$ (M^{+1}): m/z = 799.3442 Found: m/z = 799.3442.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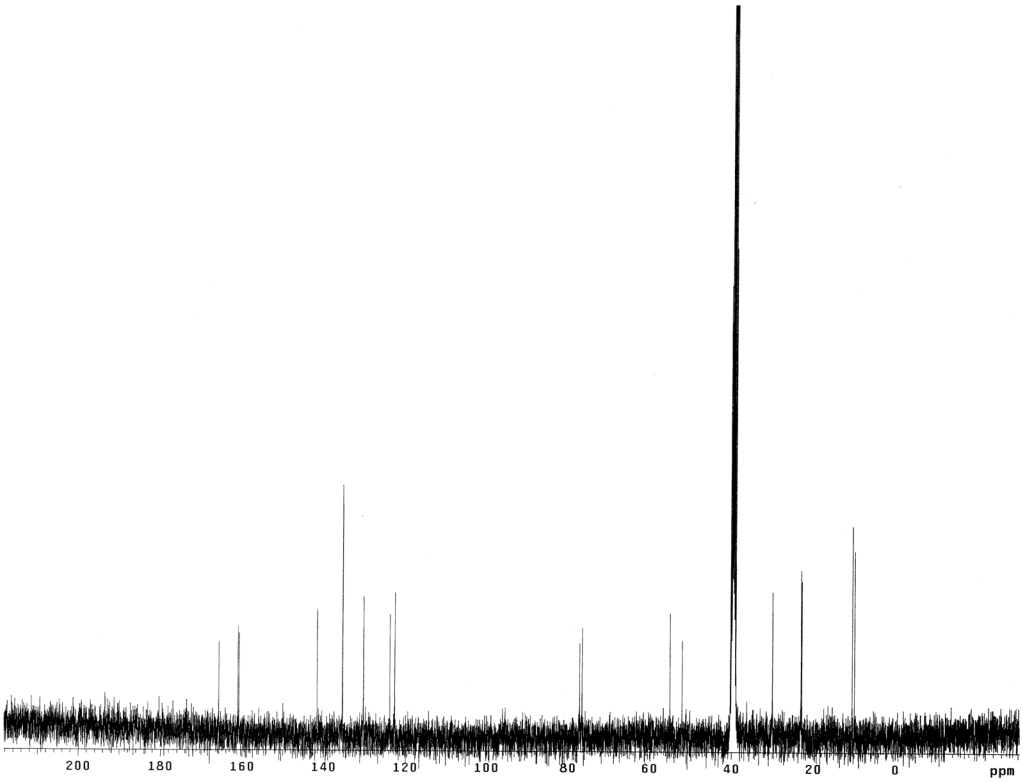
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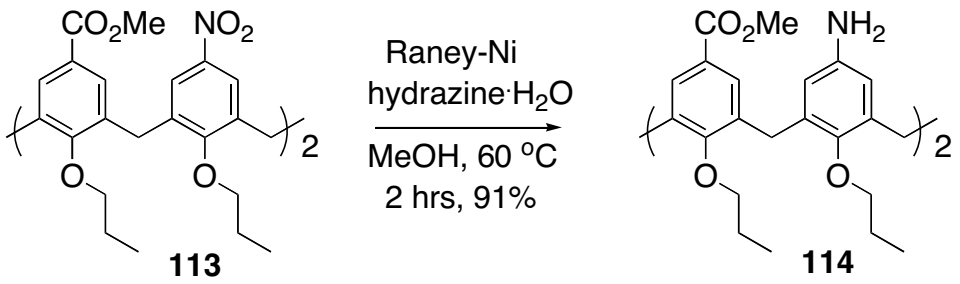
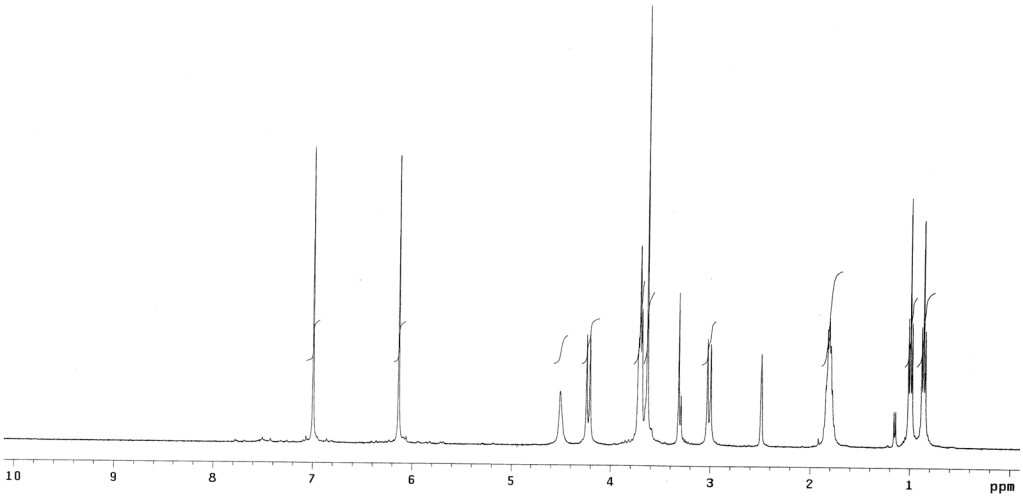


Synthesis of Diaminodicarboxymethyltetrapropoxycalix[4]arene 114[2]

Dicarboxymethyldinitrotetrapropoxycalix[4]arene **113** (400 mg, 1 eq) was stirred in methanol (50 mL) in a round bottom flask under nitrogen. The reaction was heated to 60 °C and Raney nickel (cat.) was added. Hydrazine monohydrate (12 eq) was added and the reaction was stirred rapidly. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 2 hours, the reaction cooled to room temperature and the Raney nickel was removed by filtration. The reaction was then concentrated *in vacuo* (336 mg, 91% yield). M.P. = 123-130 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 7.00 (s, 4 H), δ 6.14 (s, 4 H), δ 4.51 (br s, 4 H), δ 4.23 (d, 4 H, J = 12.8 Hz), δ 3.71 (t, 8 H, J = 6.4 Hz), δ 3.64 (s, 6 H), δ 3.01 (d, 4 H, J = 13.2 Hz), δ 1.78-1.85 (m, 8 H), δ 1.00 (t, 6 H, J = 7.3 Hz), δ 0.87 (t, 6 H, J = 7.3 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 168.2, 161.9, 151.0, 142.0, 136.3, 136.2, 130.5, 124.5, 117.7, 78.0, 77.9, 52.2, 32.1, 24.6, 24.3, 11.0, 10.8; HRMS (FAB) Calcd. for $C_{44}H_{55}N_2O_8$ (M^{+1}): m/z = 739.3958 Found: m/z = 739.3910.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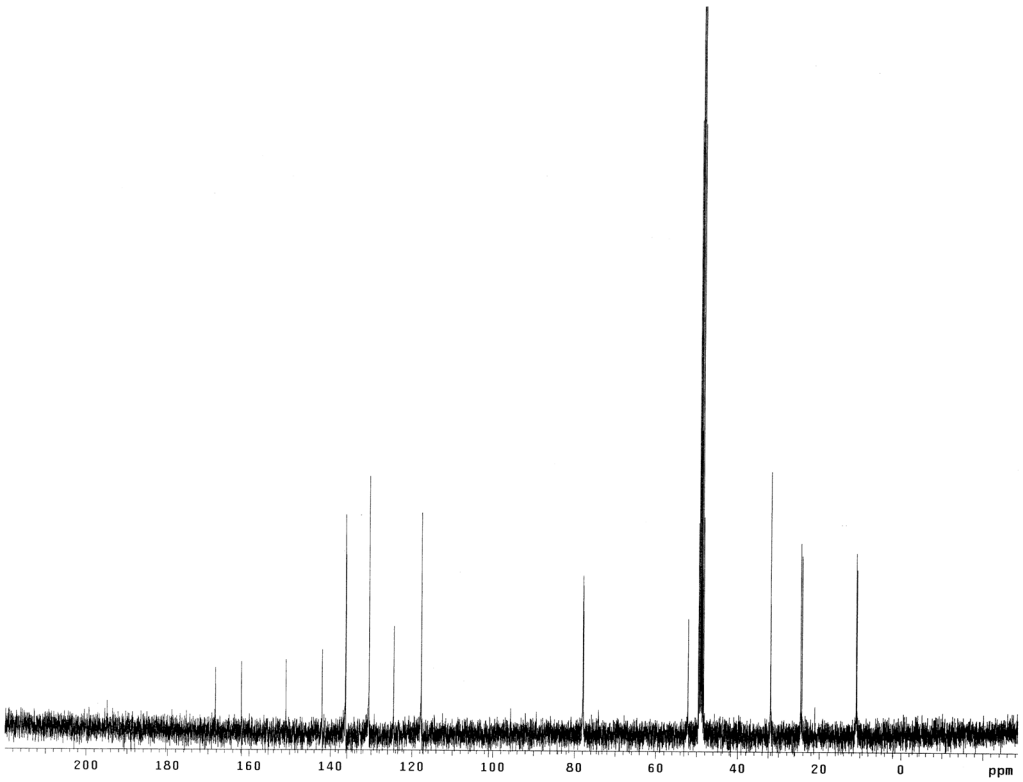
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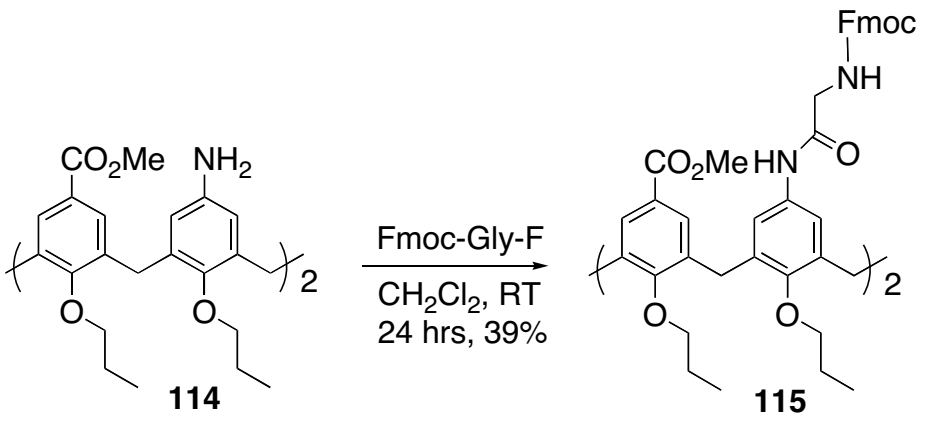
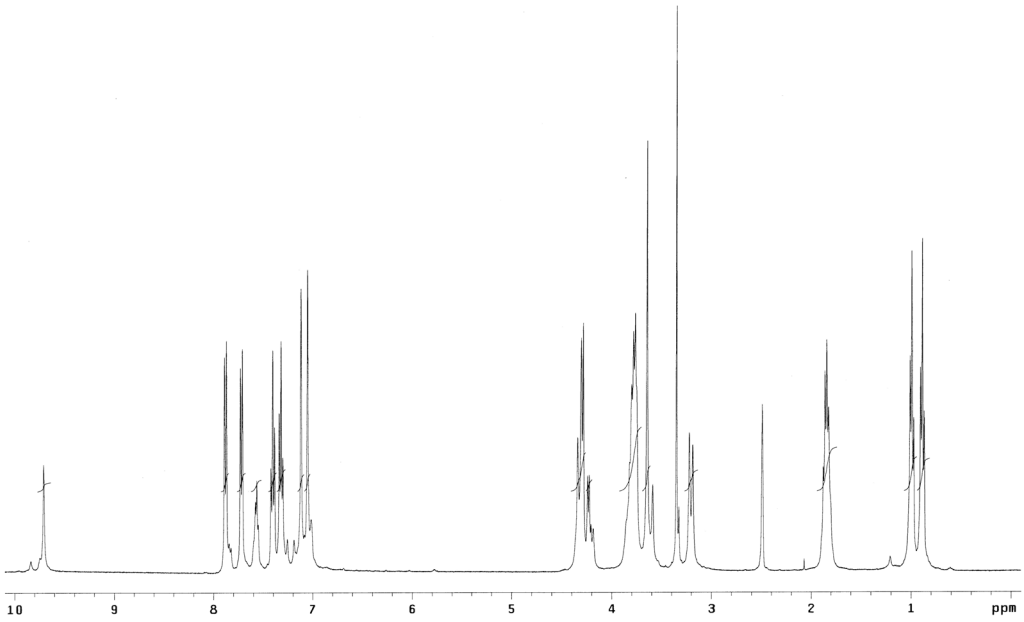


Synthesis of Dicarboxymethyldifmocglycinotetrapropoxycalix[4]arene 115

Diaminodicarboxymethyltetrapropoxycalix[4]arene **114** (50 mg, 1 eq) was dissolved in methylene chloride (5 mL) in a round bottom flask under nitrogen. Fmoc-glycine acid fluoride (5 eq) was added to the reaction and stirred overnight at room temperature. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 24 hours, the reaction was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2:1% MeOH). A tan solid was recovered (39% yield). ^{1}H NMR (400 MHz DMSO-d_6): δ 9.71 (s, 2 H), δ 7.88 (d, 4 H, J = 7.6 Hz), δ 7.72 (d, 4 H, J = 7.6 Hz), δ 7.41 (t, 4 H, J = 8.0 Hz), δ 7.32 (t, 4 H, J = 7.2 Hz), δ 7.12 (s, 4 H), δ 7.05 (s, 4 H), δ 4.34-4.23 (m, 10 H), δ 3.80-3.76 (m, 12 H), δ 3.64 (s, 6H), δ 3.20 (d, 4 H, J = 13.6 Hz), δ 1.88-1.82 (m, 8 H), δ 0.99 (t, 6 H, J = 7.2 Hz), δ 0.89 (t, 6 H, J = 7.2 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 167.4, 165.7, 159.9, 156.6, 152.3, 143.9, 140.7, 134.7, 134.4, 133.0, 128.8, 127.6, 127.1, 125.3, 123.3, 120.1, 119.7, 76.5, 76.4, 65.7, 51.5, 46.6, 43.9, 30.4, 22.9, 22.5, 10.3, 10.0; HRMS (MALDI) Calcd. for $C_{78}H_{80}N_4O_{14}$ (M^{+Na}): m/z = 1319.556 Found: m/z = 1319.5568.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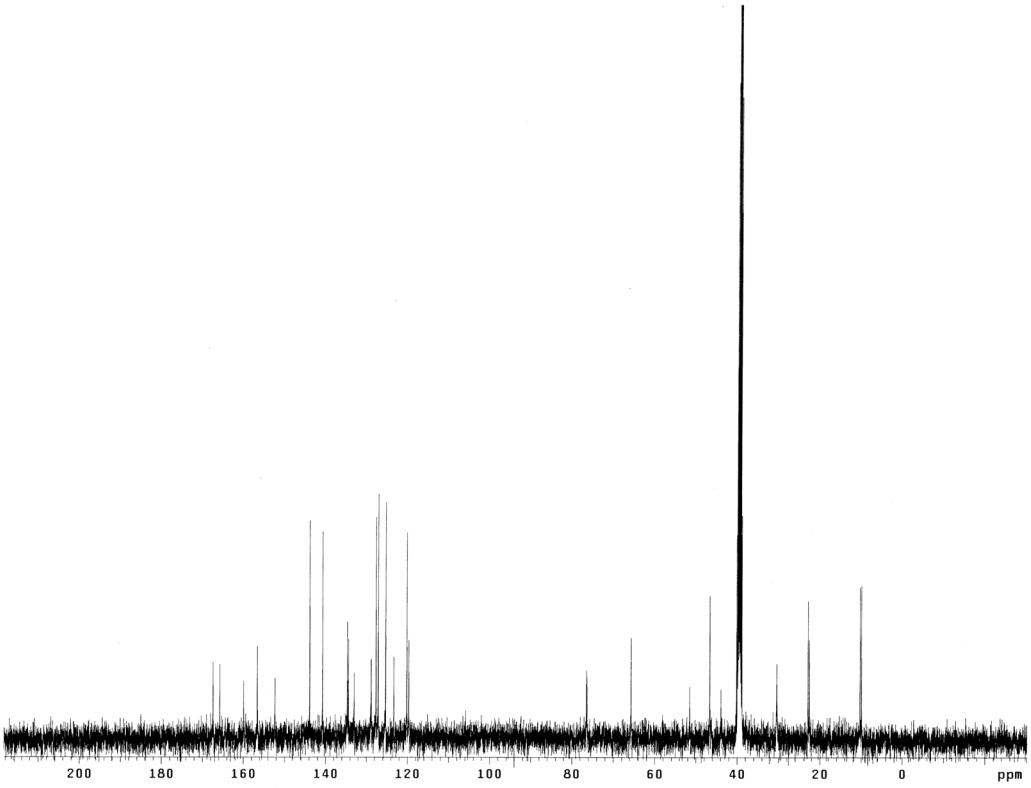
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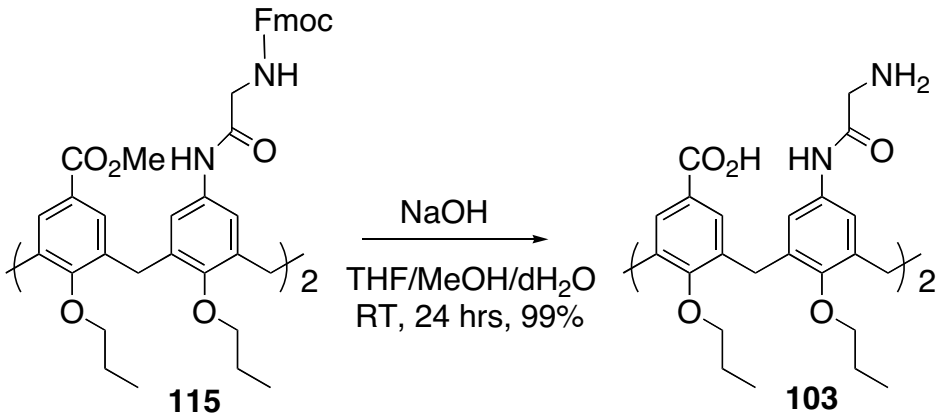
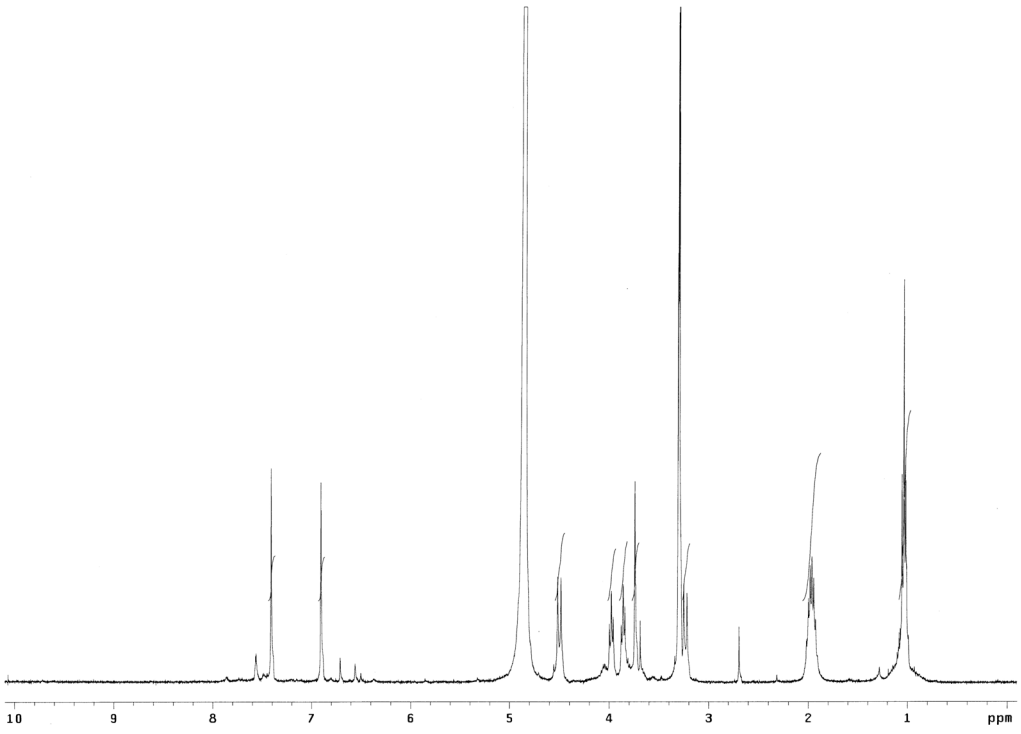


Synthesis of Dicarboxydiglycinotetrapropoxycalix[4]arene 103

Dicarboxymethyldifmocglycinotetrapropoxycalix[4]arene **115** (60 mg, 1 eq) was dissolved in THF (2.5 mL) in a round bottom flask under nitrogen. Methanol (0.25 mL) was added and stirred. Sodium hydroxide (20 eq) was dissolved in deionized water (1.0 mL) and added to the reaction and stirred at room temperature overnight. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 24 hours, the reaction was neutralized with 1 N HCl and concentrated *in vacuo*. The product was dissolved in a small amount of methanol and the undissolved salt was removed by filtration. The methanol was then concentrated *in vacuo* leaving the product. A tan solid was recovered (99% yield). M.P. = 265 °C (dec.); ^{1}H NMR (400 MHz CD_3OD): δ 7.41 (s, 4 H), δ 6.91 (s, 4 H), δ 4.50 (d, 4 H, *J* = 13.2 Hz), δ 3.98 (t, 4 H, *J* = 7.6 Hz), δ 3.86 (t, 4 H, *J* = 7.2 Hz), δ 3.74 (s, 4 H), δ 3.24 (d, 4 H, *J* = 13.2 Hz), δ 2.05-1.90 (m, 8 H), δ 1.04 (t, 12 H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, CD_3OD): δ 169.7, 162.1, 154.5, 136.4, 136.1, 133.1, 131.4, 127.0, 125.6, 121.8, 120.1, 78.2, 42.1, 31.9, 24.5, 24.4, 10.8, 10.7; HRMS (FAB): Calcd. for $C_{46}H_{57}N_4O_{10}$ (M^{+1}): *m/z* = 825.4075. Found: *m/z* = 825.4111.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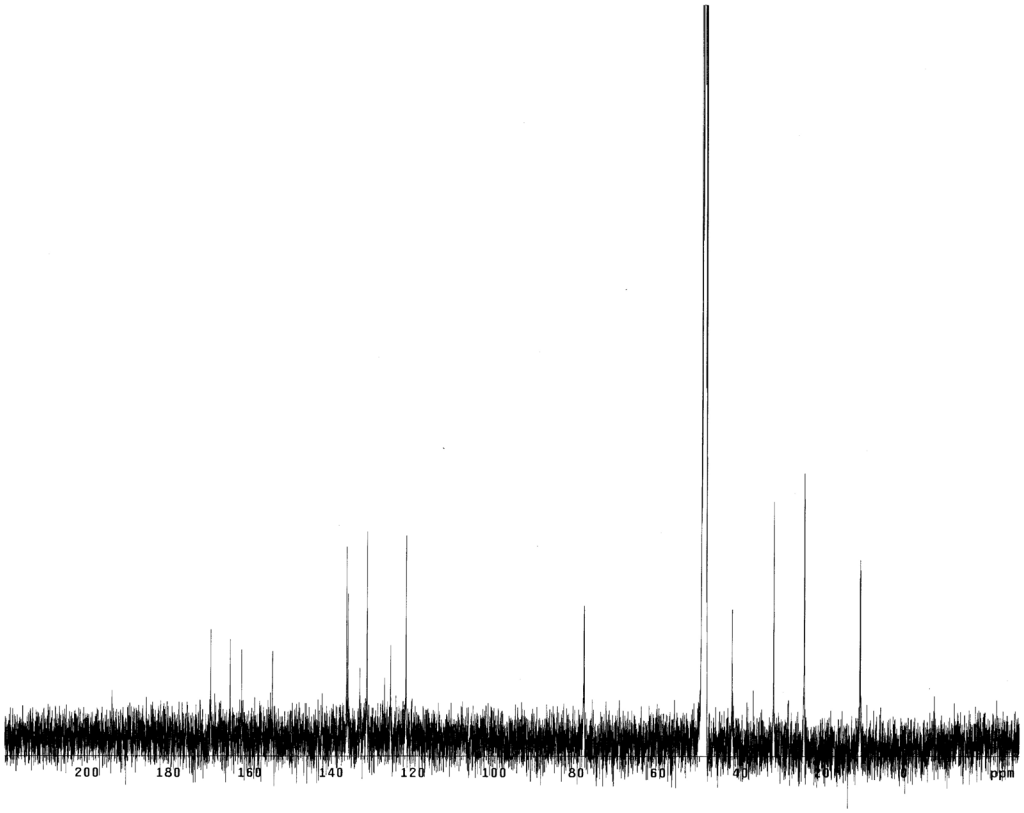
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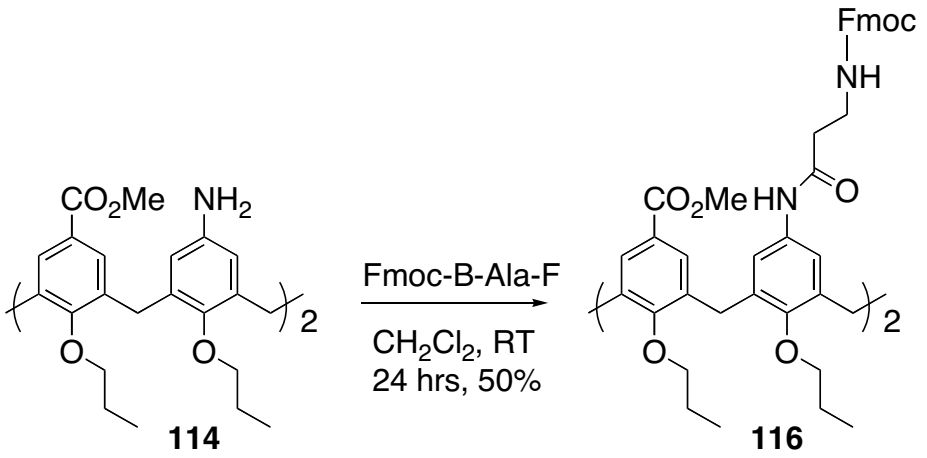
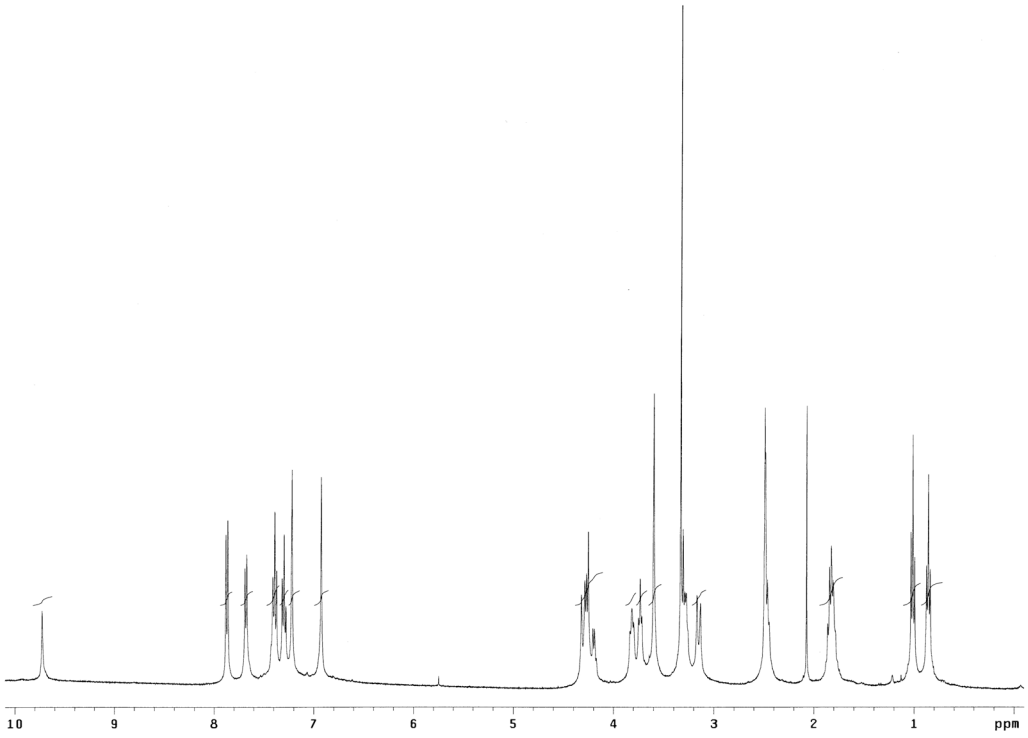


Synthesis of Dicarboxymethyldifmoc-ß-alaninotetrapropoxycalix[4]arene 116

Diaminodicarboxymethyltetrapropoxycalix[4]arene **114** (50 mg, 1 eq) was dissolved in methylene chloride (5 mL) in a round bottom flask under nitrogen. Fmoc-ß-alanine acid fluoride (5 eq) was added to the reaction and stirred overnight at room temperature. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 24 hours, the reaction was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2:1% MeOH). A tan solid was recovered (50% yield). M.P. = 136 °C (dec.); ^{1}H NMR (400 MHz DMSO-d_6): δ 9.73 (s, 2 H), δ 7.87 (d, 4 H, *J* = 7.6 Hz), δ 7.68 (d, 4 H, *J* = 7.2 Hz), δ 7.40 (t, 4 H, *J* = 7.6 Hz), δ 7.30 (t, 4 H, *J* = 7.2 Hz), δ 7.22 (s, 4 H), δ 6.93 (s, 4 H), δ 4.32-4.12 (m, 10 H), δ 3.82 (t, 4 H, *J* = 7.2 Hz), δ 3.73 (t, 4 H, *J* = 6.8 Hz), δ 3.60 (s, 6H), δ 3.29 (t, 4 H, *J* = 5.6 Hz), δ 3.15 (d, 4 H, *J* = 13.6 Hz), δ 1.86-1.78 (m, 8 H), δ 1.01 (t, 6 H, *J* = 7.6 Hz), δ 0.86 (t, 6 H, *J* = 7.6 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 168.8, 165.6, 159.7, 156.1, 152.3, 143.9, 140.7, 134.9, 134.1, 133.4, 128.6, 127.6, 127.1, 125.2, 123.2, 120.1, 119.7, 76.5, 65.4, 51.4, 46.7, 36.9, 36.5, 30.5, 22.9, 22.4, 10.4, 9.9; HRMS (FAB) Calcd. for $C_{80}H_{85}N_4O_{14}$ (M^{+1}): *m/z* = 1325.6062 Found: *m/z* = 1325.6099.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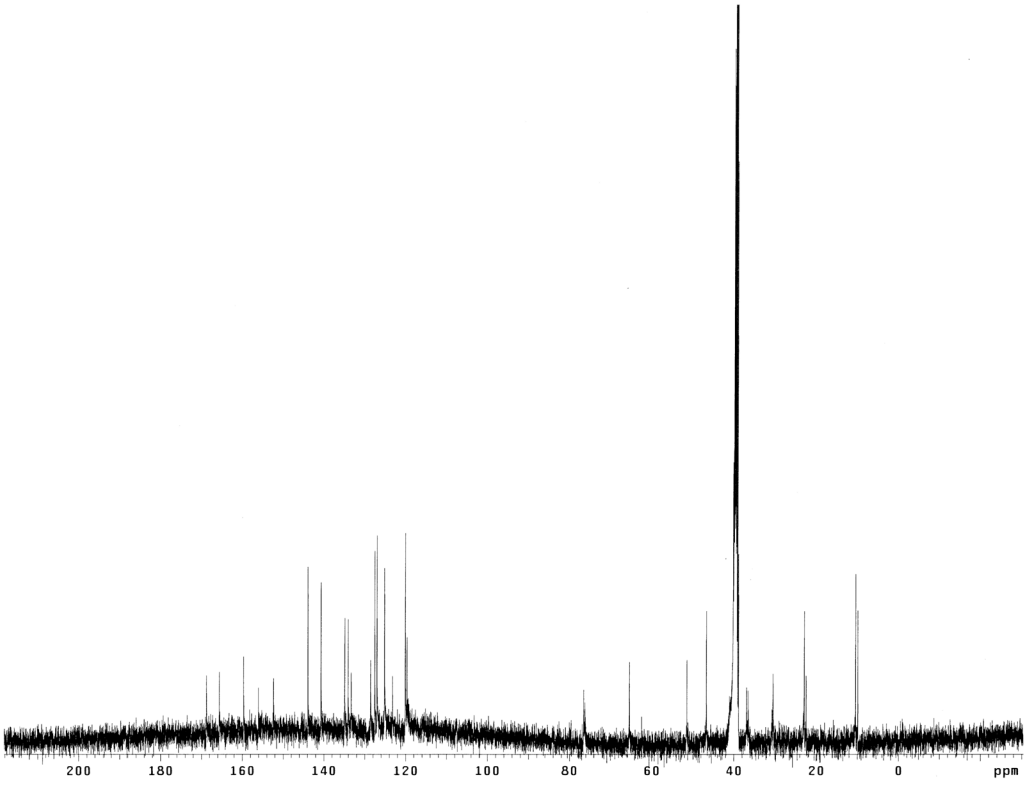
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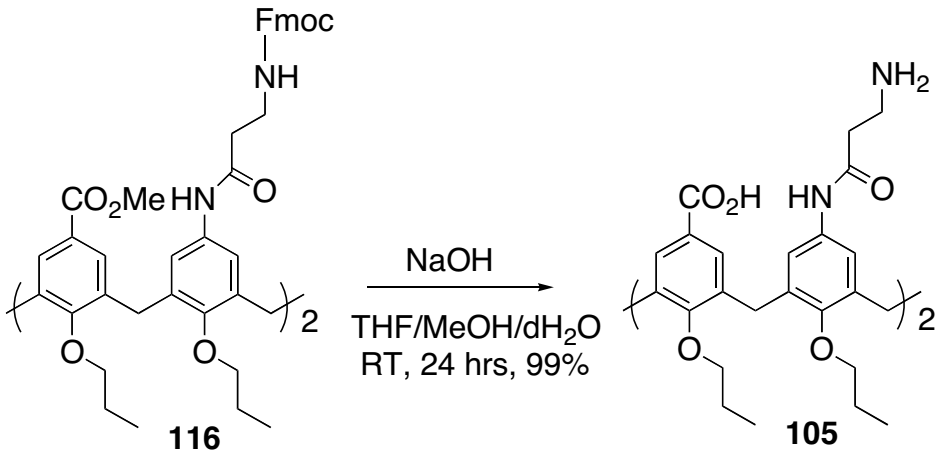
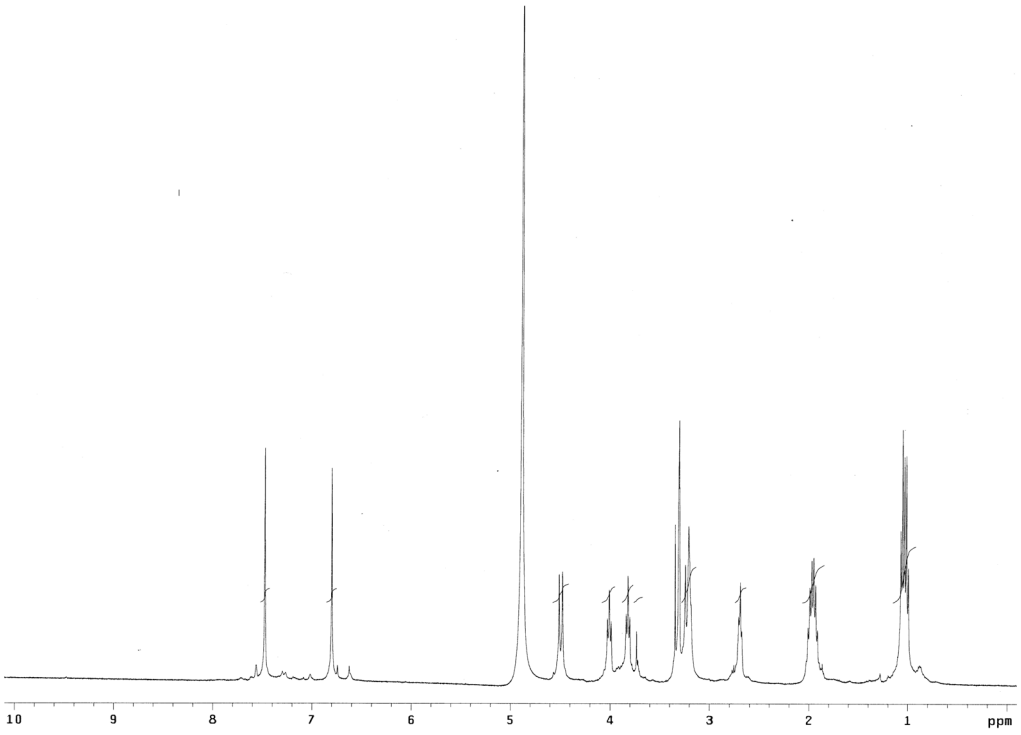


Synthesis of Dicarboxydi-ß-alaninotetrapropoxycalix[4]arene 105

Dicarboxymethyldifmoc-ß-alaninotetrapropoxycalix[4]arene **116** (60 mg, 1 eq) was dissolved in THF (2.5 mL) in a round bottom flask under nitrogen. Methanol (0.25 mL) was added and stirred. Sodium hydroxide (20 eq) was dissolved in deionized water (1.0 mL) and added to the reaction and stirred at room temperature overnight. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 24 hours, the reaction was neutralized with 1 N HCl and concentrated *in vacuo*. The product was dissolved in a small amount of methanol and the undissolved salt was removed by filtration. The methanol was then concentrated *in vacuo* leaving the product. A tan solid was recovered (99% yield). M.P. = 245 °C (dec.); ^{1}H NMR (400 MHz CD_3OD): δ 7.48 (s, 4 H), δ 6.79 (s, 4 H), δ 4.49 (d, 4 H, J = 13.2 Hz), δ 4.01 (t, 4 H, J = 7.6 Hz), δ 3.82 (t, 4 H, J = 7.6 Hz), δ 3.21-3.24 (m, 8 H), δ 2.69 (t, 4 H, J = 6.0 Hz), δ 1.93-2.01 (m, 8 H), δ 0.99-1.07 (m, 12 H); ^{13}C NMR (400 MHz, CD_3OD): δ 170.0, 169.8, 162.4, 154.2, 136.7, 135.7, 133.5, 131.5, 125.5, 121.9, 78.3, 78.2, 37.0, 33.6, 32.0, 24.4, 10.9, 10.6; HRMS (FAB) Calcd. for $C_{48}H_{61}N_4O_{10}$ (M^{+1}): m/z = 853.4388 Found: m/z = 853.4424.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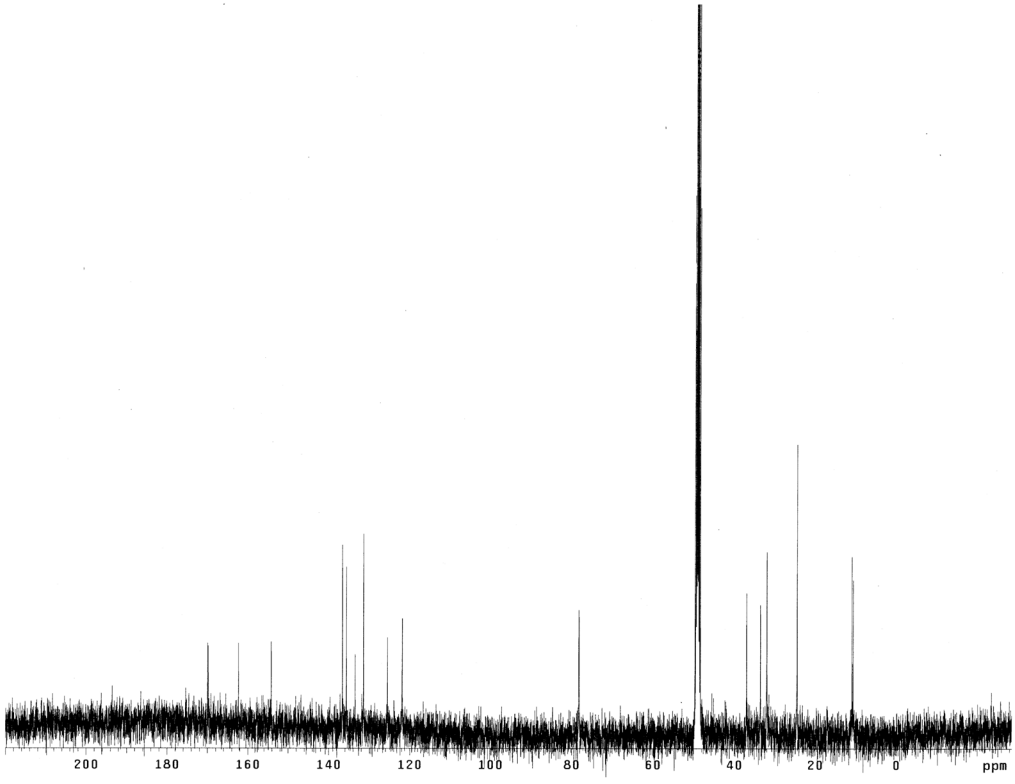
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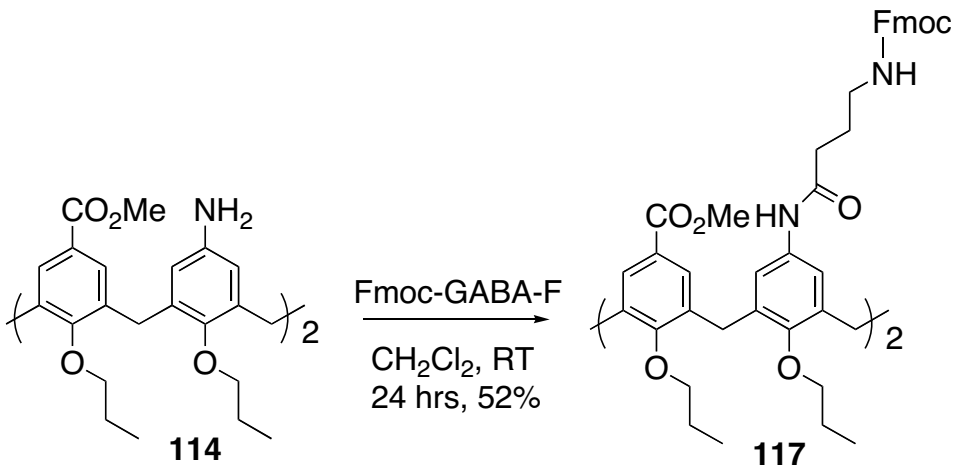
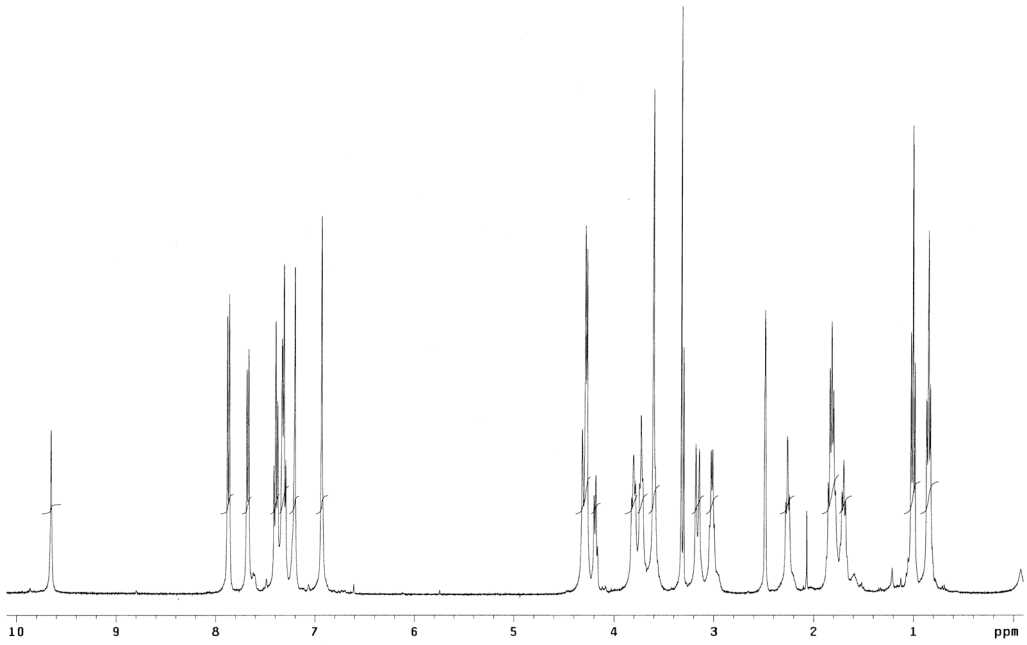


Synthesis of Dicarboxymethyldifmoc-γ-aminobutyric acid-tetrapropoxycalix[4]arene 117

Diaminodicarboxymethyltetrapropoxycalix[4]arene **114** (50 mg, 1 eq) was dissolved in methylene chloride (5 mL) in a round bottom flask under nitrogen. Fmoc-γ-aminobutyric acid fluoride (5 eq) was added to the reaction and stirred at room temperature overnight. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 24 hours, the reaction was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2:1% MeOH). A tan solid was recovered (52% yield). M.P. = 127 °C (dec.); ^{1}H NMR (400 MHz DMSO-d_6): δ 9.65 (s, 2 H), δ 7.87 (d, 4 H, *J* = 7.6 Hz), δ 7.68 (d, 4 H, *J* = 7.6 Hz), δ 7.39 (t, 4 H, *J* = 8.0 Hz), δ 7.31 (t, 4 H, *J* = 7.6 Hz), δ 7.20 (s, 4 H), δ 6.93 (s, 4 H), δ 4.32-4.19 (m, 10 H), δ 3.81 (t, 4 H, *J* = 7.2 Hz), δ 3.73 (t, 4 H, *J* = 6.8 Hz), δ 3.61 (s, 6H), δ 3.16 (d, 4 H, *J* = 13.6 Hz), δ 3.02 (q, 4 H, *J* = 5.6 Hz), δ 2.26 (t, 4 H, *J* = 7.6 Hz), δ 1.85-1.78 (m, 8 H), δ 1.70 (p, 4 H, *J* = 6.4 Hz), δ 1.01 (t, 6 H, *J* = 7.2 Hz), δ 0.85 (t, 6 H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 170.3, 165.7, 159.7, 156.1, 152.3, 143.9, 140.7, 134.9, 134.1, 133.5, 128.6, 127.6, 127.1, 125.2, 123.2, 120.1, 119.6, 76.5,

76.2, 65.2, 51.4, 46.8, 33.6, 30.4, 25.4, 22.9, 22.4, 10.4, 9.9; HRMS (FAB) Calcd. for $C_{82}H_{89}N_4O_{14}$ (M^{+1}): m/z = 1353.6375 Found: m/z = 1353.6362.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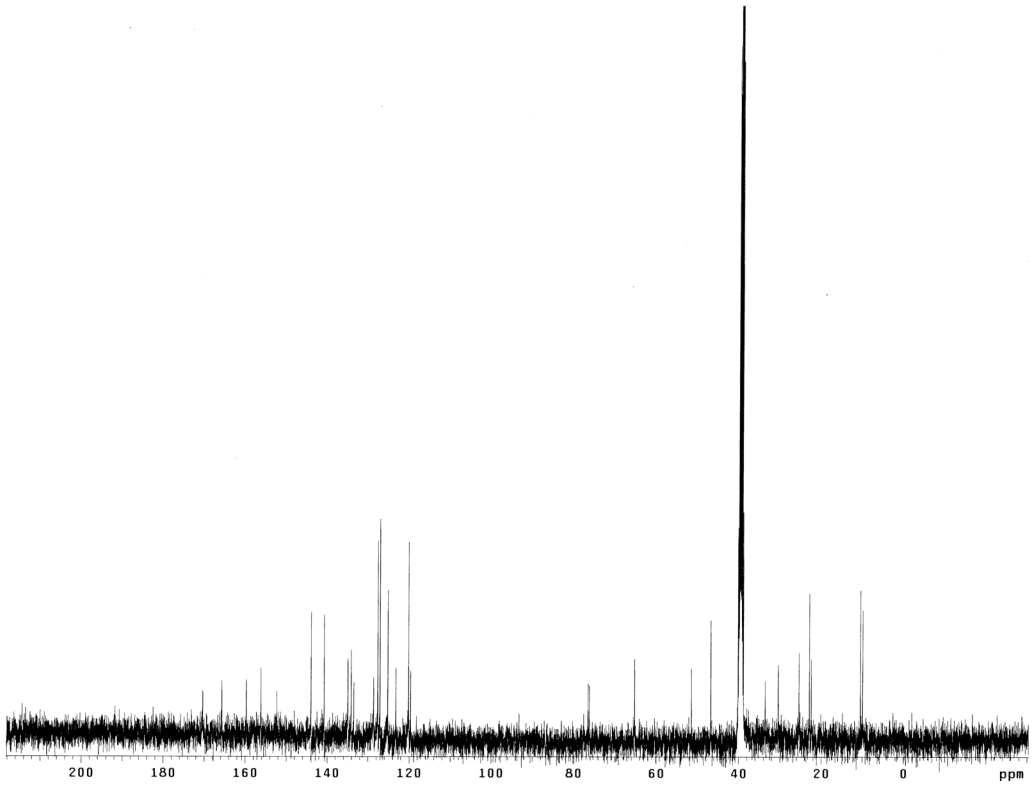
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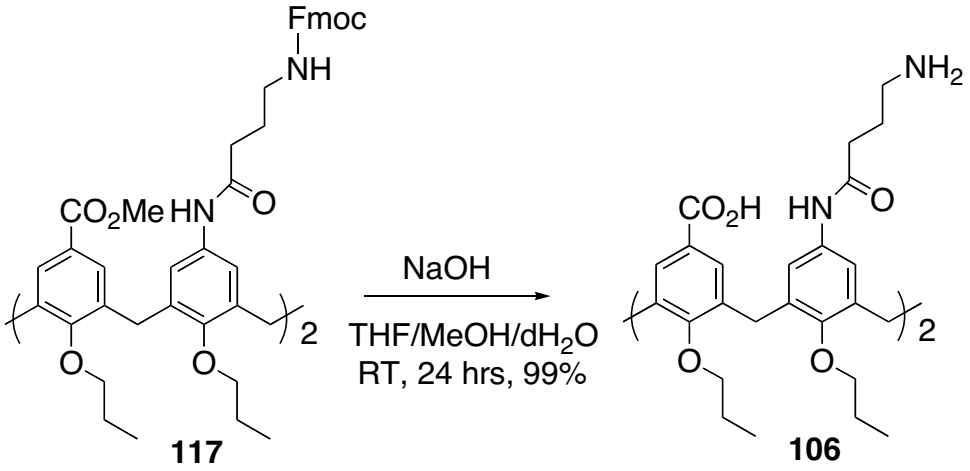
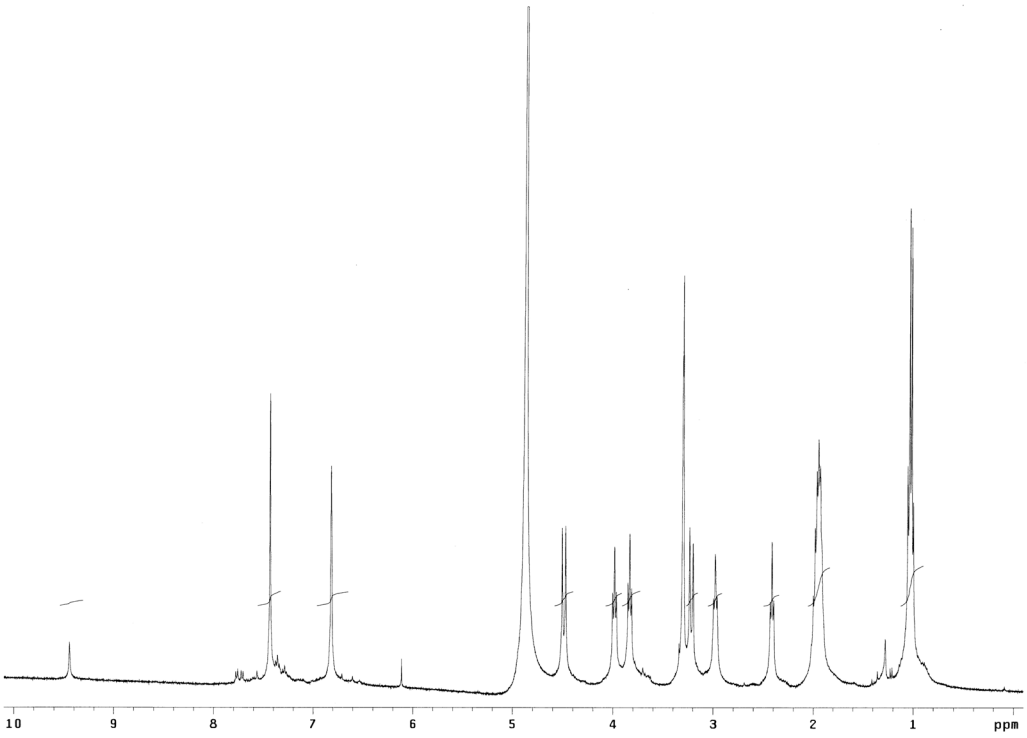


Synthesis of Dicarboxydi-γ-aminobutyric acid-tetrapropoxycalix[4]arene 106

Dicarboxymethyldifmoc-γ-aminobutyric acid-tetrapropoxycalix[4]arene **117** (60 mg, 1 eq) was dissolved in THF (2.5 mL) in a round bottom flask under nitrogen. Methanol (0.25 mL) was added and stirred. Sodium hydroxide (20 eq) was dissolved in deionized water (1.0 mL) and added to the reaction and stirred at room temperature overnight. The reaction was monitored by TLC (95:5, CH_2Cl_2:MeOH). After 24 hours, the reaction was neutralized with 1 N HCl and concentrated *in vacuo*. The product was dissolved in a small amount of methanol and the undissolved salt was removed by filtration. The methanol was then concentrated *in vacuo* leaving the product. A tan solid was recovered (99% yield). M.P. = 240 °C (dec.); ^{1}H NMR (400 MHz CD_3OD): δ 7.44 (s, 4 H), δ 6.82 (s, 4 H), δ 4.49 (d, 4 H, *J* = 13.2 Hz), δ 3.99 (t, 4H, *J* = 8.0 Hz), δ 3.83 (t, 4 H, *J* = 7.2 Hz), δ 3.22 (d, 4 H, *J* = 13.6 Hz), δ 2.98 (t, 4 H, *J* = 7.2 Hz), δ 2.41 (t, 4 H, *J* = 7.2 Hz), δ 1.93-2.00 (m, 12 H), δ 1.00-1.06 (m, 12 H); ^{13}C NMR (400 MHz, CD_3OD): δ 172.4, 169.8, 162.3, 154.3, 136.6, 135.8, 135.7, 133.7, 131.4, 125.5, 122.0, 78.2, 40.4,

34.4, 32.0, 24.5, 24.4, 24.3, 10.9, 10.7; HRMS (FAB) Calcd. for $C_{50}H_{65}N_4O_{10}$ (M^{+1}): *m*/*z* = 881.4701 Found: *m*/*z* = 881.4706.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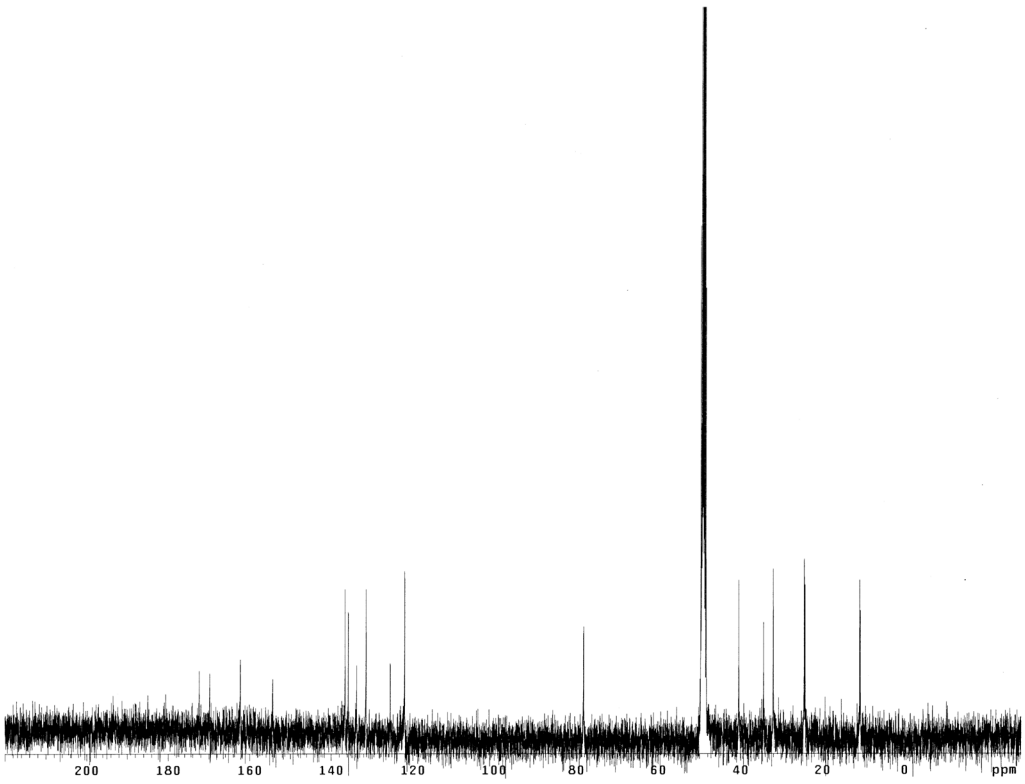
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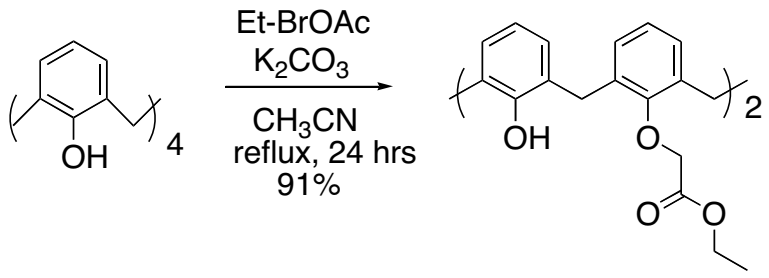
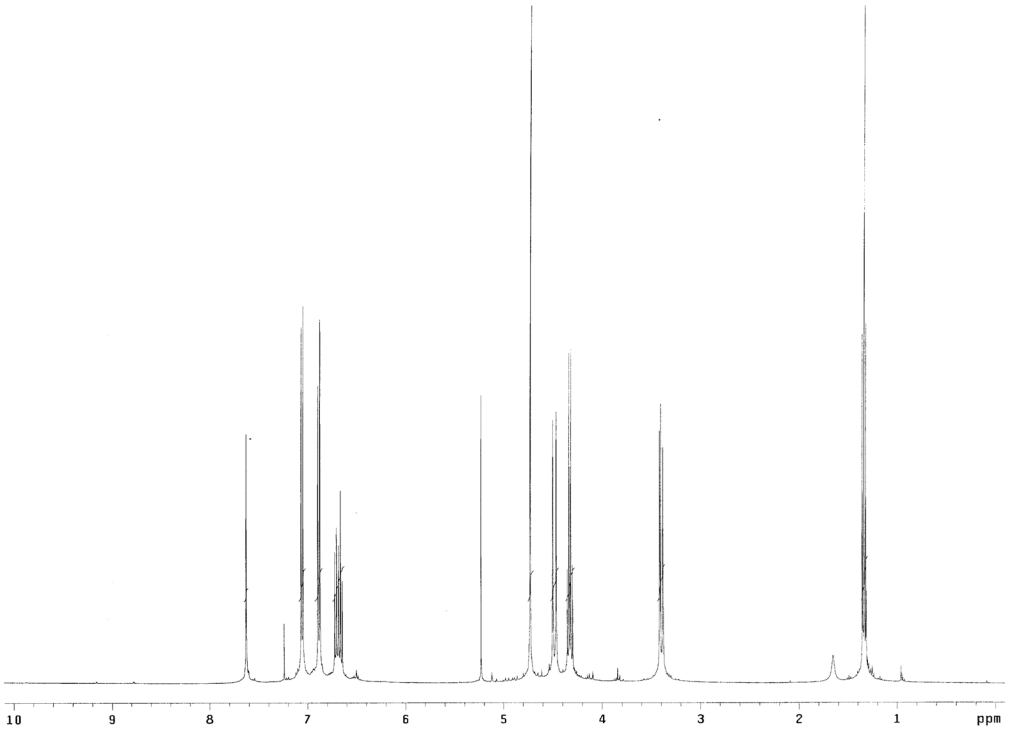


Synthesis of Diethylacetoxycalix[4]arene 143[11]

Calix[4]arene **93** (9.8 g, 1 eq) and potassium carbonate (3.5 g, 1.1 eq) were placed in a round bottom flask under nitrogen. Acetonitrile (300 mL) was added and stirred. Ethyl-bromoacetate (5.7 mL, 2.2 eq) was added and the reaction was refluxed for 24 hours. After cooling to room temperature, the reaction was filtered to remove the unreacted potassium carbonate. The solution was then concentrated *in vacuo*. The white foamy solid was redissolved in methylene chloride and washed with deionized water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The off-white solid (15 g) was recrystallized in methanol yielding white crystals (12.5 g, 91% yield). M.P. = 169-173 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.63 (s, 2 H), δ 7.06 (d, 4 H, *J* = 7.2 Hz), δ 6.88 (d, 4 H, *J* = 7.6 Hz), δ 6.72-6.64 (m, 4 H), δ 4.73 (s, 4 H), δ 4.48 (d, 4 H, *J* = 13.2 Hz), δ 4.32 (q, 4H, *J* = 6.8 Hz), δ 3.40 (d, 4 H, *J* = 13.2 Hz), δ 1.33 (t, 6 H. *J* = 6.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.8, 152.9, 152.3, 133.0, 129.1, 128.4, 128.0, 125.5, 119.0, 72.4, 61.3, 31.4, 14.0; HRMS (FAB) Calcd. for $C_{56}H_{57}O_8$ (M^{+1}): *m/z* = 598.2561 Found: *m/z* = 597.2526.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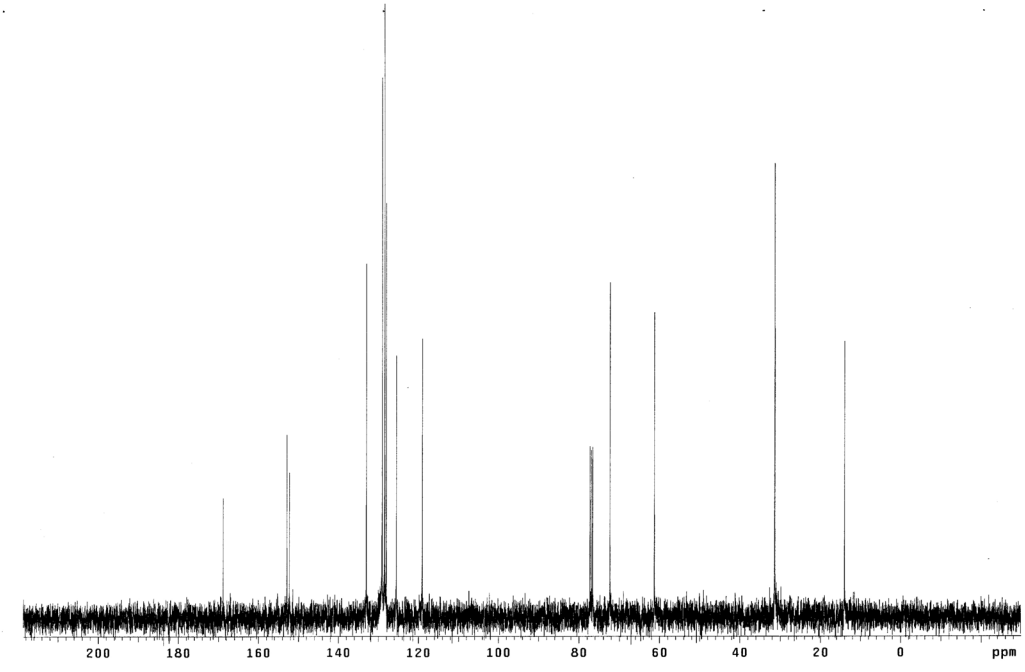
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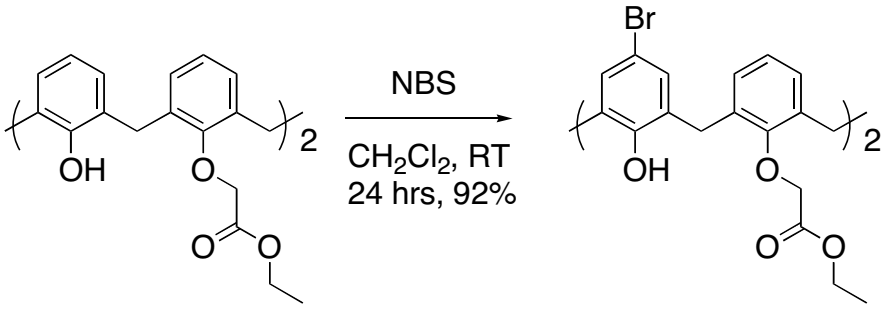
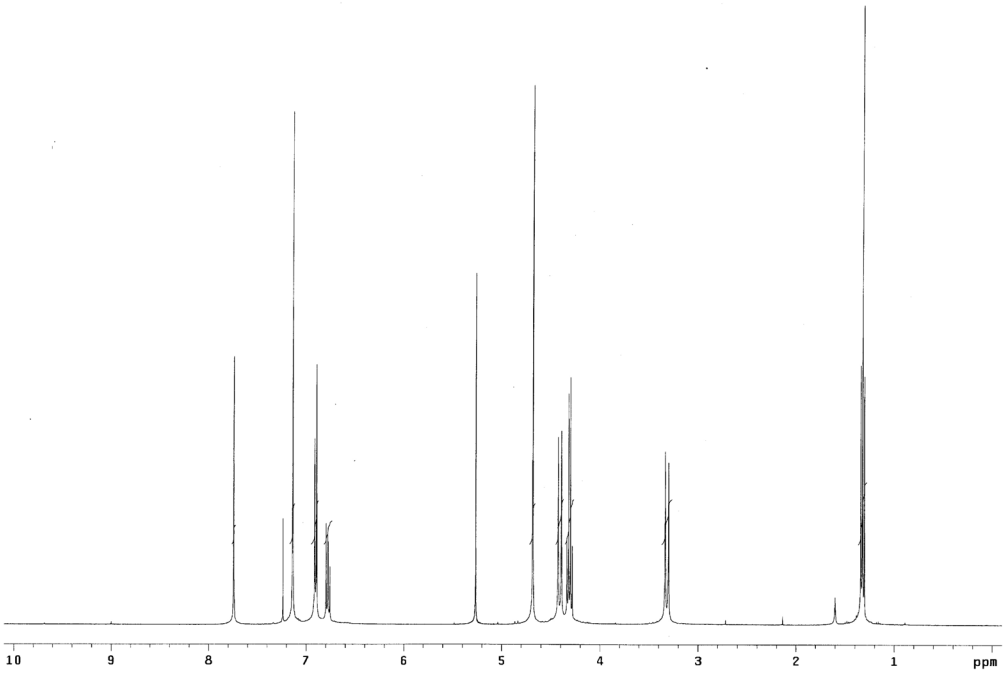


Synthesis of Dibromodiethylacetoxycalix[4]arene 144

Diethylacetoxycalix[4]arene **143** (1 g, 1eq) was dissolved in methylene chloride (20 mL) in a round bottom flask under nitrogen. *N*-Bromosuccinamide (650 mg, 2.2 eq) was added and the reaction was stirred at room temperature overnight. After 24 hours, the reaction was washed with saturated ammonium chloride, deionized water, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. A yellow solid was recovered (1.2 g, 92% yield). M.P. = 240 °C (dec.); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.74 (s, 2 H), δ 7.14 (s, 4 H), δ 6.90 (d, 4 H, J = 7.6 Hz), δ 6.80-6.78 (m, 4 H), δ 4.68 (s, 4 H), δ 4.41 (d, 4 H, J = 13.2 Hz), δ 4.31 (q, 4H, J = 7.2 Hz), δ 3.31 (d, 4 H, J = 13.2 Hz), δ 1.32 (t, 6 H. J = 7.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.7, 152.4, 152.0, 132.5, 130.8, 130.1, 129.4, 125.8, 110.6, 72.3, 61.4, 31.2, 14.1; HRMS (FAB) Calcd. for $C_{56}H_{54}O_8Br_2$ (M^+): m/z = 752.0620 Found: m/z = 752.0650.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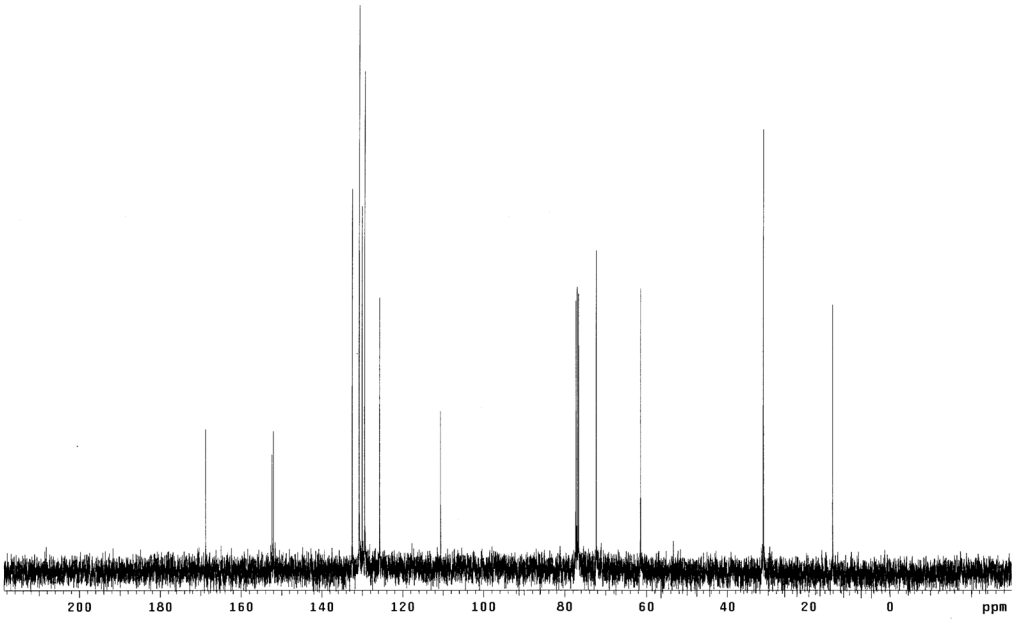
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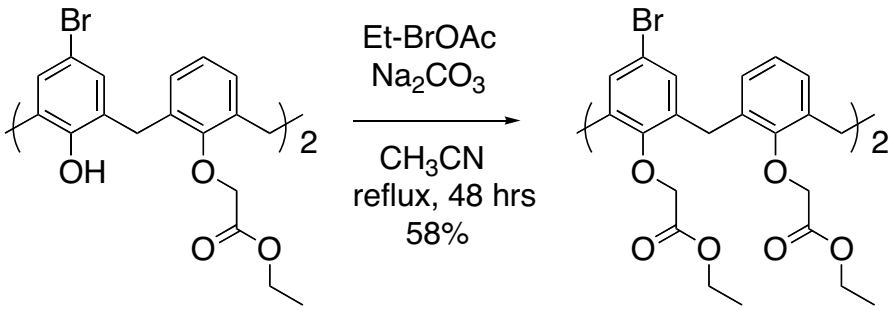
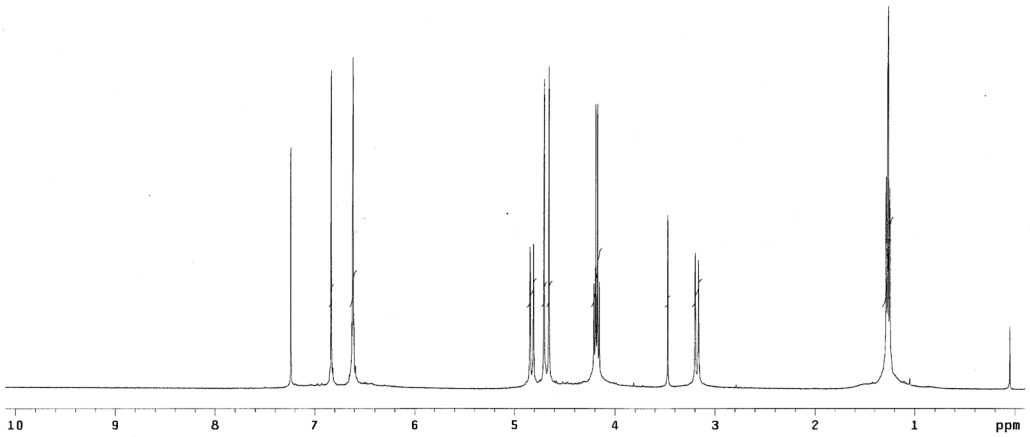


Synthesis of Dibromotetraethylacetoxycalix[4]arene 145[11]

Dibromodiethylacetoxycalix[4]arene **144** (2.1 g, 1 eq) and sodium acetate (3.0 g, 10 eq) were added to a round bottom flask under nitrogen. Acetonitrile (40 mL) was added and the reaction was stirred. Ethyl-bromoacetate (3.1 mL, 10 eq) was added and the reaction was refluxed. After 48 hours, the reaction was cooled to room temperature and filtered to remove the unreacted sodium carbonate. The solution was concentrated *in vacuo*. The red oil was redissolved in methylene chloride. Deionized water was added and vigorously stirred overnight to remove any dissolved sodium carbonate. The organic layer was separated and dried over magnesium sulfate. The organic layer was filtered and concentration *in vacuo* and recrystallized in methylene chloride/methanol. The yellow crystals (1.5 g, 58% yield) were dried *in vacuo*. M.P. = 131-133 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 6.84 (s, 4 H), δ 6.62 (s, 6 H), δ 4.83 (d, 4 H, J = 13.6 Hz), δ 4.70 (s, 4 H), δ 4.66 (s, 4 H), δ 4.18 (q, 4H, J = 7.2 Hz), δ 3.18 (d, 4 H, J = 13.6 Hz), δ 1.27 (t, 12 H. J = 6.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.9, 155.6, 155.1, 136.9, 133.7, 131.2, 128.7, 123.4, 115.6, 71.3, 71.2, 60.6, 60.6, 31.3, 14.2; HRMS (FAB) Calcd. for $C_{44}H_{46}O_{12}Br_2$ (M^+): m/z = 924.1356 Found: m/z = 924.1340.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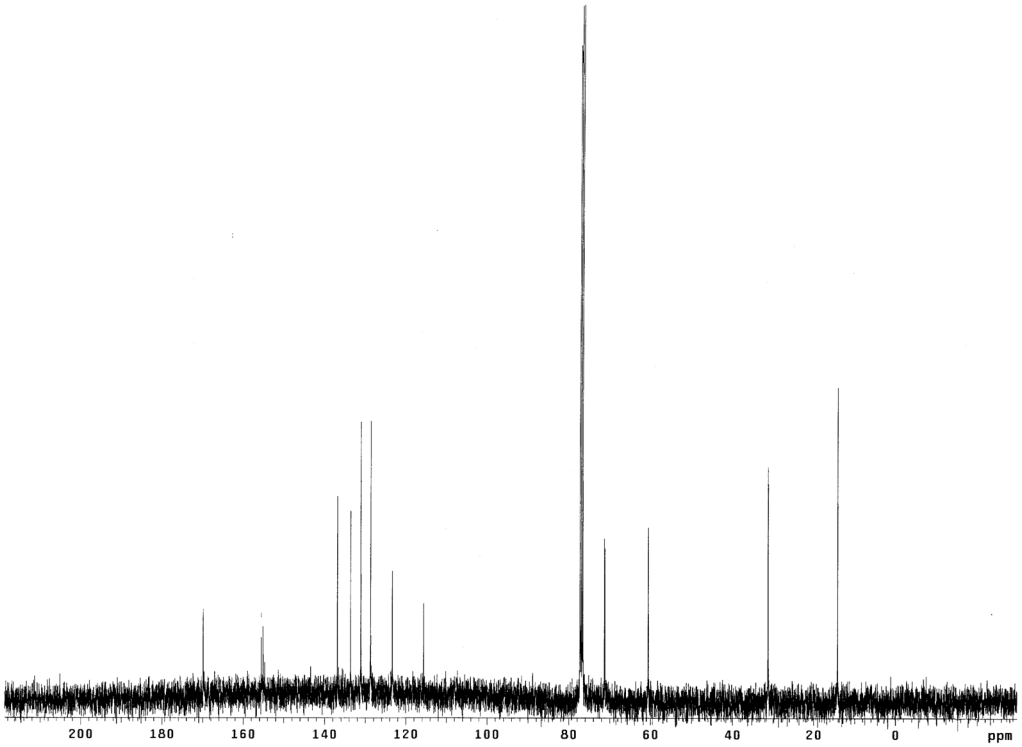
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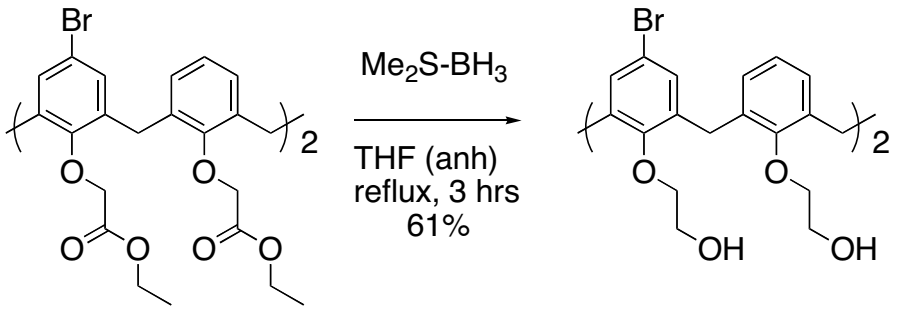
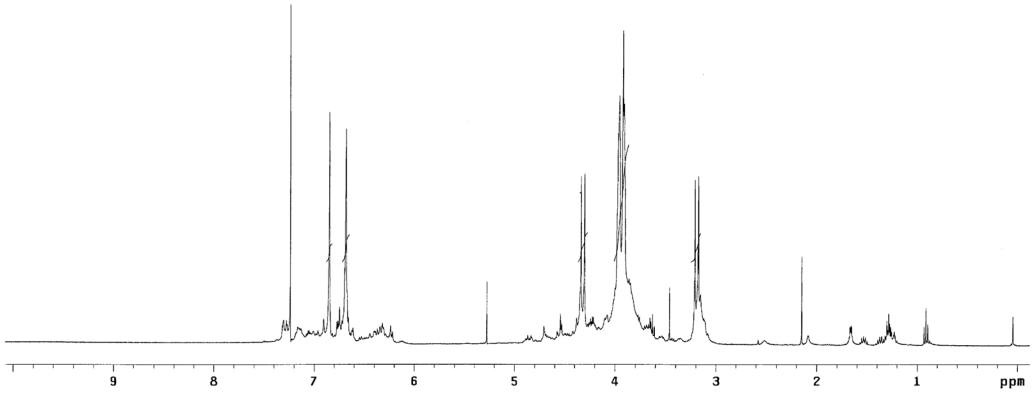


Synthesis of Dibromotetrahydroxyethylcalix[4]arene 141[12]

Dibromotetraethylacetoxycalix[4]arene **145** (500 mg, 1 eq) was dissolved in anhydrous THF (10 mL) in a round bottom flask under nitrogen. Borane-methyl sulfide complex (2M, 2 mL, 7.5 eq) was added dropwise and while the reaction was stirred. After addition of the borane-methyl sulfide complex, the reaction was refluxed and monitored by TLC (10:1, CH_2Cl_2:MeOH). After 3 hours, the reaction was cooled to room temperature and quenched slowly with saturated sodium carbonate with lots of bubbling. The solution was then acidified with concentrated hydrochloric acid and the product was extracted with methylene chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product (390 mg) was purified by column chromatography (CH_2Cl_2/ 5% methanol) to give an off-white solid (250 mg, 61% yield). M.P. 127 °C (dec.); ^{1}H NMR (400 MHz $CDCl_3$): δ 6.86 (s, 4 H), δ 6.69 (s, 6 H), δ 4.33 (d, 4 H, J = 13.6 Hz), δ 3.97 (s, 4 H), δ 3.93 (s, 4 H), δ 3.20 (d, 4 H, J = 13.6 Hz; ^{13}C NMR (400 MHz, $CDCl_3$): δ 154.8, 154.2, 136.8, 133.7, 131.4, 129.0, 123.8, 116.1, 78.0, 78.0, 61.5, 61.4, 30.1; HRMS (FAB) Calcd. for $C_{36}H_{39}O_8Br_2$ (M^{+1}): m/z = 757.1011 Found: m/z = 757.0955.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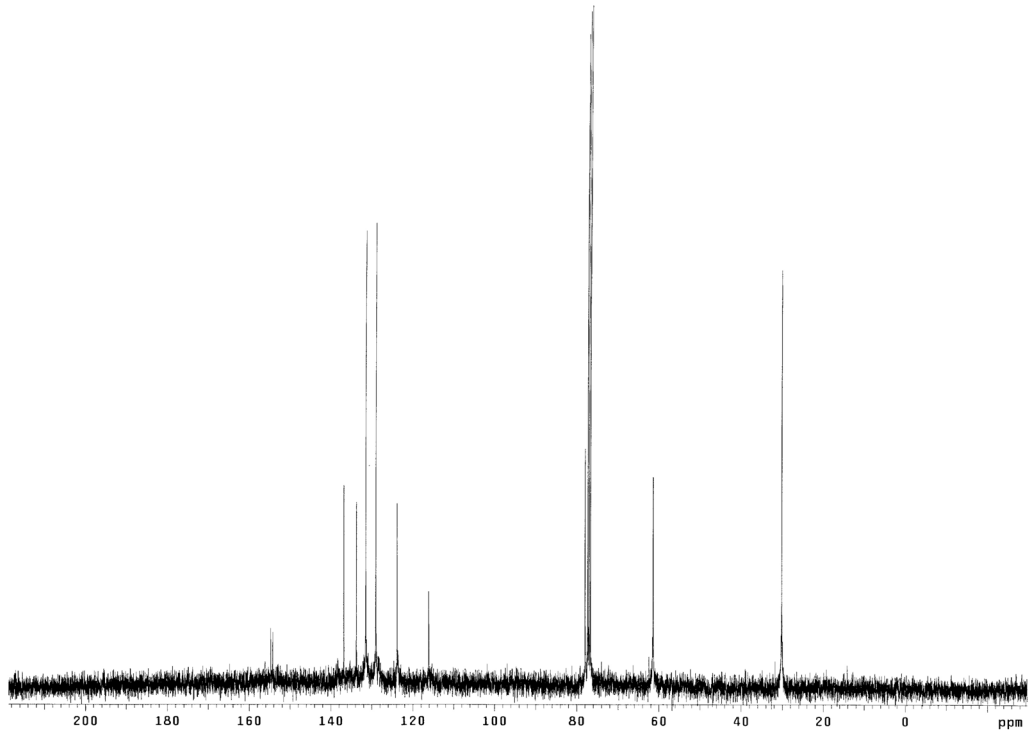
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3.3 References

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VITA

Joshua Sidney Sasine was born in Atlanta, GA on March 4, 1976 to Jeff and Janice Sasine. He has an older sister, Vicki, and a younger brother, Greg. He grew up in Atlanta and graduated from Riverwood High School in May 1994. He went on to the University of Florida where he worked as an undergraduate researcher for Dr. M. A. Battiste. He graduated with highest honors in chemistry in December 1999. After graduating, he had a six month internship in organic synthesis with Dr. John Hyatt at Eastman Chemical Company. He married his wife, Dana, on July 24, 1999 and then went on to graduate school at the Georgia Institute of Technology. While at Georgia Tech, he had two children, Matthew (4 years old) and Elizabeth (2 years old). He received his Ph.D. in organic chemistry in May 2005 under the guidance of Dr. Suzanne Shuker.